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(54) Title: VARIANTS OF ALTERNATIVE SPLICING

(57) Abstract: The present invention concerns novel variants, amino acid and nucleic acid sequences obtained by alternative splicing of known sequences, expression vectors and host cells containing the variants' nucleic acid sequence, and antibodies reactive with the variants' products. The invention also concerns pharmaceutical compositions containing any of the above as well as methods of detection. A preferred example is the angiotensin converting enzyme (ACE) variant.

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VARIANTS OF ALTERNATIVE SPLICING

FIELD OF THE INVENTION

The present invention concerns novel nucleic acid sequences, vectors and host cells containing them, amino acid sequences encoded by said sequences, and antibodies reactive with said amino acid sequences, as well as pharmaceutical compositions comprising any of the above. The present invention further concerns methods for screening for candidate activators or deactivators utilizing said amino acid sequences.

BACKGROUND OF THE INVENTION

Alternative splicing (AS) is an important regulatory mechanism in higher eukaryotes (P.A. Sharp, Cell 77, 805-8152 (1994). It is thought to be one of the most important mechanisms for differential expression related to tissue or development stage specificity. It is known to play a major role in numerous biological systems, including human antibody responses, and sex determination in Drosophila, (S. Stamm, M.Q. Zhang, T.G. Marr and D.M. Helfman, Nucleic Acids Research 22, 1515-1526 (1994); B. Chabot, Trends Genet. 12, 472-478 (1996); R.E. Breitbart, A. Andreadis, B. Nadal-Ginard, Annual Rev. Biochem., 56, 467-495 (1987); C.W. Smith, J.G. Patton, B. Nadal-Ginard, Annu. Rev. Genet., 27, 527-577 (1989)).

Until recently it was commonly believed that alternative splicing existed in only a small fraction of genes (about 5%). A recent observation based on literature survey of known genes revises this conservative estimate to as high as an estimate that at least 30% of human genes are alternatively spliced (M.S. Gelfand, I. Dubchak, I. Draluk and M. Zorn, *Nucleic Acids Research* 27, 301-302 (1999). The importance of the actual frequency of this phenomenon lies not only

in the direct impact on the number of proteins created (100,000 human genes, for example, would be translated to a much higher number of proteins), but also in the diversity of functionality derived from the process.

Several mechanisms at different stages may be held responsible for the complexity of higher eukaryote which include: alternative splicing at the transcription level, RNA editing at the post-transcriptional level, and post-translational modifications are the ones characterized to date.

Angiotensin I-converting enzyme (ACE) is a peptidyldipeptide hydrolase that is located mainly on the luminal surface of vascular endothelial cells but also in cells derived from the monocyte-macrophage system. Physiologically, ACE is a key enzyme in the renin-angiotensin system, converting angiotensin I into the potent vasopressor angiotensin II and also inactivating the vasodilator bradykinin.

Increased serum ACE activity (SACE) has been reported in pathologies involving stimulation of the monocytic cell line, primarily granulomatous diseases. Sarcoidosis is the most frequent and the better studied of these diseases; high SACE is not only a well-established marker for the diagnosis but is also a useful tool for following its course and evaluating the effect of therapy of this disease.

SACE can also be increased in nonsarcoidotic pulmonary granulomatous diseases such as silicosis and asbestosis, in extrathoracic granulomatous pathologies such as Gauchers disease and leprosis, and, to a lesser extent, in nongranulomatous disorders such as hyperthyroidism or cholestasis.

Decreased SACE has been reported in vascular pathologies involving an endothelial abnormality, such as deep vein thrombosis, and in endothelium dysfunctions related to the toxicity of chemo- and radiotherapy used in cancers, leukemias, and hematopoietic or organ transplantations.

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SACE is also of interest for monitoring arterial hypertension treated with specific synthetic ACE inhibitors.

Various methods have been developed for determining SACE activities. spectrophotometric used is the The widely hippuryl-histidyl-leucine as substrate. Fluorimetric and radiochemical assays using both classic and novel substrates have been proposed, but they are time consuming, require special apparatus, and are not suited to automation. Kinetic spectrophotometry of furylacryloyl-phenylalanyl-glycyl-glycine hydrolysis is now used extensively because it is easy to automatize.

Information obtained in the last decade indicates that angiotensin II increases the production of several autocrine factors, including transforming growth factor beta1 (TGF-beta1), tumor necrosis factor-alpha (TNF-alpha), and platelet-derived growth factor A chain (PDGF). Angiotensin also increases the release of other growth factors such as endothelin, platelet-activating factor 15 (PAF), and interleukin 6. In addition, it increases the "activity" of nuclear factor-kappaB (NF-kappaB) and the synthesis of angiotensinogen. The emerging picture indicates that the actions of angiotensin II may be related to factors that are released or upregulated by angiotensin II, possibly through NF-kappaB.

GLOSSARY

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In the following description and claims use will be made, at times, with a variety of terms, and the meaning of such terms as they should be construed in accordance with the invention is as follows:

"Variant nucleic acid sequence" - the sequence shown in any one of SEQ ID 25 NO: 1 to SEQ ID NO: 87, native and known genes. It should be emphasized that the novel variants of the present invention are naturally occurring sequences resulting from alternative splicing of genes and not merely truncated, mutated or fragmented forms of known sequences which are artificially produced.

"Angiotensin converting enzyme variant (ACEV)" - a sequence shown in SEQ ID NO: 57 or 85 sequences having at least 90% identity (see below) to said sequence and fragments (see below) of the above sequences of least 20 b.p. long. These sequences are sequences coding for a novel, naturally occurring, alternative splice variants of the mouse angiotensin converting enzyme which convert angiotensin I to angiotensin II by release of the terminal His-Lew resulting in increase of vasoconstrictor activity of angiotensin.

"Variant product – also referred at times as the "variant protein" or "variant polypeptide" – is an amino acid sequence encoded by the variant nucleic acid sequence SEQ ID NO: 88 to SEQ ID NO: 174.

"ACEV product or ACEV protein"— amino acid coded by the ACEV nucleic acid which is a naturally occurring mRNA sequence obtained as a result of alternative splicing of the ACE gene. The amino acid sequence may be a peptide, a protein, as well as peptides or proteins having chemically modified amino acids (see below) such as a glycopeptide or glycoprotein. The variant products are shown in SEQ ID NO: 144 or 172. The term also includes homologies (see below) of said sequences in which one or more amino acids has been added, deleted, substituted (see below) or chemically modified (see below) as well as fragments (see below) of this sequence having at least 10 amino acids. The above two products may be secreted.

"Nucleic acid sequence" – a sequence composed of DNA nucleotides, RNA nucleotides or a combination of both types and may include natural nucleotides, chemically modified nucleotides and synthetic nucleotides.

"Amino acid sequence" – a sequence composed of any one of the 20 naturally appearing amino acids, amino acids which have been chemically modified (see below), or composed of synthetic amino acids.

"Fragment of variant nucleic acid sequence" and "fragment of ACEV nucleic acid sequence" - novel short stretch of nucleic acid sequences of at least 20 b.p., which does not appear as a continuous stretch in the original nucleic acid sequence (see below). The fragment may be a sequence which was previously 5 undescribed in the context of the published RNA and which affects the amino acid sequence encoded by the known gene. For example, where the variant nucleic includes a sequence which was not included in the original sequence (for example a sequence which was an intron in the original sequence) the fragment may contain said additional sequence. The fragment may also be a region which 10 is not an intron, which was not present in the original sequence. For example where the variant lacks a non-terminal region which was present in the original sequence. The two stretches of nucleotides spanning this region (upstream and downstream) are brought together by splicing in the variant, but are spaced from each by the spliced out region in the original sequence and are thus not 15 continuous in the original sequence. A continuous stretch of nucleic acids comprising said two sparing stretches of nucleotides is not present in the original sequence and thus falls under the definition of fragment.

"Fragments of variant products" - novel amino acid sequences coded by the "fragment of variant nucleic acid sequence" or "fragment of ACEV nucleic acid sequence" defined above.

"Homologues of variants" – amino acid sequences of variants in which one or more amino acids has been added, deleted or replaced. The addition, deletion or replacement should be in the regions or adjacent to regions where the variant differs from the original sequence (see below).

"Conservative substitution" - refers to the substitution of an amino acid in one class by an amino acid of the same class, where a class is defined by common physicochemical amino acid side chain properties and high substitution

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frequencies in homologous proteins found in nature, as determined, for example, by a standard Dayhoff frequency exchange matrix or BLOSUM matrix. [Six general classes of amino acid side chains have been categorized and include: Class I (Cys); Class II (Ser, Thr, Pro, Ala, Gly); Class III (Asn, Asp, Gln, Glu); Class IV (His, Arg, Lys); Class V (Ile, Leu, Val, Met); and Class VI (Phe, Tyr, Trp). For example, substitution of an Asp for another class III residue such as Asn, Gln, or Glu, is a conservative substitution.

"Non-conservative substitution" - refers to the substitution of an amino acid in one class with an amino acid from another class; for example, substitution of an Ala, a class II residue, with a class III residue such as Asp, Asn, Glu, or Gln.

"Chemically modified" - when referring to the product of the invention, means a product (protein) where at least one of its amino acid resides is modified either by natural processes, such as processing or other post-translational modifications, or by chemical modification techniques which are well known in the art. Among the numerous known modifications typical, but not exclusive examples include: acetylation, acylation, amidation, ADP-ribosylation, glycosylation, GPI anchor formation, covalent attachment of a lipid or lipid derivative, methylation, myristlyation, pegylation, prenylation, phosphorylation, ubiqutination, or any similar process.

"Biologically active" - refers to the variant product having some sort of biological activity, for example, some physiologically measurable effect on target cells, molecules or tissues.

"Immunologically active" defines the capability of a natural, recombinant or synthetic variant product, or any fragment thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies. Thus, for example, an immunologically active fragment of variant product

denotes a fragment which retains some or all of the immunological properties of the variant product, e.g. can bind specific anti-variant product antibodies or which can elicit an immune response which will generate such antibodies or cause proliferation of specific immune cells which produce variant.

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"Optimal alignment" - is defined as an alignment giving the highest percent identity score. Such alignment can be performed using a variety of commercially available sequence analysis programs, such as the local alignment program LALIGN using a ktup of 1, default parameters and the default PAM. A preferred alignment is the one performed using the CLUSTAL-W program from MacVector (TM), operated with an open gap penalty of 10.0, an extended gap penalty of 0.1, and a BLOSUM similarity matrix. If a gap needs to be inserted into a first sequence to optimally align it with a second sequence, the percent identity is calculated using only the residues that are paired with a corresponding amino acid residue (i.e., the calculation does not consider residues in the second sequences that are in the "gap" of the first sequence). In case of alignments of known gene sequences with that of the new variant, the optimal alignment invariably included aligning the identical parts of both sequences together, then keeping apart and unaligned the sections of the sequences that differ one from the other.

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"Having at least 90% identity" - with respect to two amino acid or nucleic acid sequence sequences, refers to the percentage of residues that are identical in the two sequences when the sequences are optimally aligned. Thus, 90% amino acid 25 sequence identity means that 90% of the amino acids in two or more optimally aligned polypeptide sequences are identical, however this definition explicitly excludes sequences which are 100% identical with the original sequence from which the variant of the invention was varied.

"Isolated nucleic acid molecule having an variant nucleic acid sequence" - is a nucleic acid molecule that includes the coding variant nucleic acid sequence. Said isolated nucleic acid molecule may include the variant nucleic acid sequence as an independent insert; may include the variant nucleic acid sequence fused to an additional coding sequences, encoding together a fusion protein in which the variant coding sequence is the dominant coding sequence (for example, the additional coding sequence may code for a signal peptide); the variant nucleic acid sequence may be in combination with non-coding sequences, e.g., introns or control elements, such as promoter and terminator elements or 5' and/or 3' untranslated regions, effective for expression of the coding sequence in a suitable host; or may be a vector in which the variant protein coding sequence is a heterologous.

"Expression vector" - refers to vectors that have the ability to incorporate and express heterologous DNA fragments in a foreign cell. Many prokaryotic and eukaryotic expression vectors are known and/or commercially available. Selection of appropriate expression vectors is within the knowledge of those having skill in the art.

"Deletion" - is a change in either nucleotide or amino acid sequence in which one or more nucleotides or amino acid residues, respectively, are absent.

"Insertion" or "addition" - is that change in a nucleotide or amino acid sequence which has resulted in the addition of one or more nucleotides or amino acid residues, respectively, as compared to the naturally occurring sequence.

"Substitution" - replacement of one or more nucleotides or amino acids by different nucleotides or amino acids, respectively. As regards amino acid sequences the substitution may be conservative or non-conservative.

"Antibody" - refers to IgG, IgM, IgD, IgA, or IgG antibody. The definition includes polyclonal antibodies or monoclonal antibodies. This term refers to whole antibodies or fragments of the antibodies comprising the antigen-binding domain of the anti-variant product antibodies, e.g. antibodies without the Fc portion, single chain antibodies, fragments consisting of essentially only the variable, antigen-binding domain of the antibody, etc.

Distinguishing antibody" – an antibody capable of binding to the variant product and not the original amino acid sequence from which it has been varied, or an antibody capable of binding to the original nucleic acid sequence and not to the variant production.

"Activator" - as used herein, refers to a molecule which mimics the effect of the natural variant product or at times even increases or prolongs the duration of the biological activity of said product, as compared to that induced by the natural product. The mechanism may be by any mechanism known to prolonging activities of biological molecules such as binding to receptors; prolonging the lifetime of the molecules; increasing the activity of the molecules on its target; increasing the affinity of molecules to its receptor; inhibiting degradation or proteolysis of the molecules, or mimicking the biological activity of the variants on their targets, etc. Activators may be polypeptides, nucleic acids, carbohydrates, lipids, or derivatives thereof, or any other molecules which can bind to and activate the variant product.

"Deactivator" or ("Inhibitor") - refers to a molecule which modulates the activity of the variant product in an opposite manner to that of the activator, by decreasing or shortening the duration of the biological activity of the variant product. This may be done by any mechanism known to deactivate or inhibit biological molecules such as block of the receptor, block of active site, competition on binding site in target, enhancement of degradation, etc.

Deactivators may be polypeptides, nucleic acids, carbohydrates, lipids, or derivatives thereof, or any other molecules which bind to and modulate the activity of said product.

- "Treating a disease" refers to administering a therapeutic substance effective to ameliorate symptoms associated with a disease, to lessen the severity or cure the disease, or to prevent the disease from occurring.
- "Detection" refers to a method of detection of a disease, disorder, pathological or normal condition. This term may refer to detection of a predisposition to a disease as well as for establishing the prognosis of the patient by determining the severity of the disease.
- "Probe" the variant nucleic acid sequence, or a sequence complementary
 therewith, when used to detect presence of other similar sequences in a sample.
 The detection is carried out by identification of hybridization complexes between the probe and the assayed sequence. The probe may be attached to a solid support or to a detectable label.
- "Original sequence" the amino acid or nucleic acid sequence from which the variant of the invention have been varied as a result of alternative slicing.

SUMMARY OF THE INVENTION

The present invention is based on the finding of several novel, naturally occurring splice variants, which are naturally occurring sequences obtained by alternative splicing of known genes. The novel splice variants of the invention are not merely truncated forms, fragments or mutations of known genes, but rather novel sequences which naturally occur within the body of individuals.

In particular the present invention concerns variants of alternative splice variants of angiotensin converting enzyme (ACEV).

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The term "alternative splicing" in the context of the present invention and claims refers to: intron inclusion, exon exclusion, addition or deletion of terminal sequences in the variant as compared to the original sequences, as well as to the possibility of "intron retention". Intron retention is an intermediate stage in the processing of RNA transcripts, where prior to production of fully processed mRNA the intron (naturally spliced in the original sequence) is retained in the variant. These intermediately processed RNAs may have physiological significance and are also within the scope of the invention.

The novel variant products of the invention, including the ACEV-variant (ACEV), may have the same physiological activity as the original peptide from which they have been varied (although perhaps at a different level); may have an opposite physiological activity from the activity featured by the original peptide from which they are varied; may have a completely different, unrelated activity to the activity of the original from which they are varied; or alternatively may have no activity at all and this may lead to various diseases or pathological conditions. The novel variants of the invention may differ from the original sequence, from which they were varied by alternative splicing, by physiological properties not relating directly to their activities such as: tissue localization, temporal pattern of expression, rate of clearance, rate of degradation, manner of up- or down regulation, association with co-factors and cellular elements etc.

The novel variants may also serve for detection purposes, i.e. their presence or level may be indicative of a disease, disorder, pathological or normal condition or alternatively the ratio between the level variants and the level original peptide from which they were varied, or the ratio to other variants may be indicative to a disease, disorder, pathological or normal condition.

For example, for detectional purposes, it is possible to establish differential expression of various variants in various tissues. A certain variant may be expressed mainly in one tissue, while the original sequence from which it has been varied, or another variant may, be expressed mainly in another tissue. Understanding of the distribution of the variants in various tissues may be helpful

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in basic research, for understanding the physiological function of the genes as well as may help in targeting pharmaceuticals or developing pharmaceuticals.

The study of the variants may also be helpful to distinguish various stages in the life cycles of the same type of cells which may also be helpful for development of pharmaceuticals for various pathological conditions in which cell cycles is non-normal, notably cancer.

Detection of various diseases in accordance with the invention is especially useful for detection of diseases which are associated with the function, (over function, under function, or malfunction) of proteins of the original sequence from which each variant of the invention has been obtained by alternative splicing. A list of the original proteins are given in the "Detailed Description" part of the specification. Thus, for example, if variant of SEQ ID NO: 3 is obtained from an original sequence which is coagulation factor XII, this sequence may be used to detect diseases involving excessive or diminished blood coagulation.

Thus the detection may by determination of the presence or the level of expression of the variant within a specific cell population, comprising said presence or level between various cell types in a tissue, between different tissues and between individuals.

Where the variant in the angiotensin converting enzyme (ACEV) the detection may be used for detection (including disposition) of one of the following diseases.

Cardiovascular diseases:

Including hypertension, neurological damage due to cerebral circulatory disorders, peripheral vascular diseases, arteriosclerosis, heart and kidney diseases relating to blood pressure, erection problems and migraine problems relating to circulation functions, heart failures (including recurrent infraction in patients with left ventricular dysfunction), acute phase of myocardial infarction, coronary arterial thrombosis and cardial insufficiency.

Renal diseases:

Hypertension adrenal injury (particularly in patients with type I or II diabetes), diabetic nepropathy, renal function deterioration in glomerular diseases

Muscular diseases:

Diseases involving growth of smooth muscle cells such as hypertrophy.

Immune disorders:

Various autoimmune diseases and diseases involving inflammatory mechanisms, for example, autoimmune manifestation affects in sarcoidosis, generation of immune complex nephritis, autoimmune encephatomyelitis, marker for chronic fatigue-immune dysfunction syndrome.

Multiple sclerosis:

Cancer:

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Especially those cancers effected by different growth factors including endothelia, platelet-activating factor (PAF) and interleukin 6. Examples of such cancers are tumors of the vascular system, and leukemias.

Diabetes:

<u>Sarcoidosis</u> – a disease of unknown origin characterized by the formation of granulomatous lesions that appear especially in the liver, lungs, skin and lymph nodes.

20 Nonarcoidotic Pulmonary Granulomatous Diseases:

Such as silicosis and asbestosis, in extrathoracic granulomatous pathologies such as Gauchers disease and leprosis, and, to a lesser extent, in nongranulomatous disorders such as hyperthyroidism or cholestasis. (increased sACE)

25 Vascular Pathologies Involving An Endothelial Abnormality:

Deep vein thrombosis, and in endothelium dysfunctions related to the toxicity of chemo- and radiotherapy used in cancers, leukemias, and hematopoietic or organ transplantations.

Thus the present invention provides by its first aspect, a novel isolated nucleic acid molecule comprising or consisting of any one of the coding sequence

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SEQ ID NO: 1 to SEQ ID NO: 87, fragments of said coding sequence having at least 20 nucleic acids (provided that said fragments are continuous stretches of nucleotides not present in the original sequence from which the variant was varied), or a molecule comprising a sequence having at least 90%, identity to SEQ ID NO: 1 to SEQ ID NO: 87, provided that the molecule is not completely identical to the original sequence from which the variant was varied. In particular, the above variant is that of SEQ ID NO: 57 or SEQ ID NO: 85 being the ACEV nucleic acid sequence.

The present invention further provides a protein or polypeptide comprising or consisting of an amino acid sequence encoded by any of the above nucleic acid sequences, termed herein "variant product", for example, an amino acid sequence having the sequence as depicted in any one of SEQ ID NO: 88 to SEQ ID NO: 174, fragments of the above amino acid sequence having a length of at least 10 amino acids coded by the above fragments of the nucleic acid sequences, as well as homologues of the above amino acid sequences in which one or more of the amino acid residues has been substituted (by conservative or non-conservative substitution) added, deleted, or chemically modified. In particular, the product is the amino acid sequence of the ACEV as depicted in SEQ ID NO: 144 or 172.

The deletions, insertions and modifications should be in regions, or adjacent to regions, wherein the variant differs from the original sequence.

For example, where the variant is different from the original sequence by addition of a short stretch of 10 amino acids, in the terminal or non-terminal portion of the peptide, the invention also concerns homologues of that variant where the additional short stretch is altered for example, it includes only 8 additional amino acids, includes 13 additional amino acids, or it includes 10 additional amino acids, however some of them being conservative or non-conservative substitutes of the original additional 10 amino acids of the novel variants. In all cases the changes in the homolog, as compared to the original sequence, are in the same regions where the variant differs from the original sequence, or in regions adjacent to said region.

Another example is where the variant lacks a non-terminal region (for example of 20 amino acids) which is present in the original sequence (due for example to exon exclusion). The homologues may lack in the same region only 17 amino acids or 23 amino acids. Again the deletion is in the same region where the variant lacks a sequence as compared to the original sequence, or in a region adjacent thereto.

It should be appreciated that once a man versed in the art's attention is directed to the importance of a specific region, due to the fact that this region differs in the variant as compared to the original sequence, there is no problem in derivating said specific region by addition to it, deleting from it, or substituting some amino acids in it. Thus homologues of variants which are derivated from the variant by changes (deletion, addition, substitution) only in said region as well as in regions adjacent to it are also a part of the present invention. Generally, if the variant is distinguished from the original sequence by some sort of physiological activity, then the homolog is distinguished from the original sequence in essentially the same manner.

The present invention further provides nucleic acid molecule comprising or consisting of a sequence which encodes the above amino acid sequences, (including the fragments and homologues of the amino acid sequences and in particular the ACEV amino acid sequence). Due to the degenerative nature of the genetic code, a plurality of alternative nucleic acid, beyond those depicted in any one of SEQ ID NO: 1 to SEQ ID NO: 87, can code for the amino acid sequence of the invention. Those alternative nucleic acid sequences which code for the same amino acid sequences codes by the sequence SEQ ID NO: 1 to SEQ ID NO: 87 are also an aspect of the of the present invention.

The present invention further provides expression vectors and cloning vectors comprising any of the above nucleic acid sequences, as well as host cells transfected by said vectors.

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The present invention still further provides pharmaceutical compositions comprising, as an active ingredient, said nucleic acid molecules, said expression vectors, or said protein or polypeptide.

These pharmaceutical compositions are suitable for the treatment of diseases and pathological conditions, which can be ameliorated or cured by raising the level of any one of the variant products of the invention. In particular, those diseases are diseases which are associated with malfunction or under function of the original sequence (for example, given in the "Detailed Description" part of the specification). Thus for example, SEQ ID NO: 3 and sequences encoded thereby may be used to treat diseases associated with coagulation of blood.

By a second aspect, the present invention provides a nucleic acid molecule comprising or consisting of a non-coding sequence which is complementary to that of any one of SEQ ID NO: 1 to SEQ ID NO: 87, or complementary to a sequence having at least 90% identity to said sequence (with the proviso added above) or a 15 fragment of said two sequences (according to the above definition of fragment). The complementary sequence may be a DNA sequence which hybridizes with any one of SEQ of ID NO: 1 to SEQ ID NO: 87 or hybridizes to a portion of that sequence having a length sufficient to inhibit the transcription of the complementary sequence. The complementary sequence may be a DNA sequence 20 which can be transcribed into an mRNA being an antisense to the mRNA transcribed from any one of SEQ ID NO: 1 to SEQ ID NO: 87 or into an mRNA which is an antisense to a fragment of the mRNA transcribed from any one of SEQ ID NO: 1 to SEQ ID NO: 87 which has a length sufficient to hybridize with the mRNA transcribed from SEQ ID NO: 1 to SEQ ID NO: 87, so as to inhibit its 25 translation. The complementary sequence may also be the mRNA or the fragment of the mRNA itself.

The nucleic acids of the second aspect of the invention may be used for therapeutic or diagnostic applications for example as probes used for the detection of the variants of the invention. The presence of the variant transcript or the level of the variant transcript may be indicative of a multitude of diseases, disorders and

various pathological as well as normal conditions for example, as indicated above for the variants in general, and for the ACEV in particular. In addition or alternatively, the ratio of the level of the transcripts of the variants of the invention may also be compared to that of the transcripts of the original sequences from which have been varied, or to the level of transcript of other variants, and said ratio may be indicative to a multitude of diseases, disorders and various pathological and normal conditions.

The present invention also provides expression vectors comprising any one of the above defined complementary nucleic acid sequences and host cells transfected with said nucleic acid sequences or vectors, being complementary to those specified in the first aspect of the invention.

The invention also provides anti-variant product antibodies, namely antibodies directed against the variant product which specifically bind to said variant product. Said antibodies are useful both for diagnostic and therapeutic purposes. For example said antibody may be as an active ingredient in a pharmaceutical composition as will be explained below.

The present invention also provides pharmaceutical compositions comprising, as an active ingredient, the nucleic acid molecules which comprise or consist of said complementary sequences, or of a vector comprising said complementary sequences. The pharmaceutical composition thus provides pharmaceutical compositions comprising, as an active ingredient, said anti-variant product antibodies.

The pharmaceutical compositions comprising said anti-variant product antibodies or the nucleic acid molecule comprising said complementary sequence, are suitable for the treatment of diseases and pathological conditions where a therapeutically beneficial effect may be achieved by neutralizing the variant (either at the transcript or product level) or decreasing the amount of the variant product or blocking its binding to its target, for example, by the neutralizing effect of the antibodies, or by the effect of the antisense mRNA in decreasing the expression level of the variant sequence.

Examples of diseases which can be treated either with ACEV sequence, an expression vector comprising that sequence, a sequence complementary to the ACEV sequence, an expression vector comprising said complementary sequence, ACEV product or an antibody to the product is any one of the diseases mentioned 5 in connection with the detection aspect above.

According to the third aspect of the invention the present invention provides methods for detecting the level of the transcript (mRNA) of said variant product in a body fluid sample, or in a specific tissue sample, for example by use of probes comprising or consisting of said coding sequences; as well as methods for detecting levels of expression of said product in tissue, e.g. by the use of antibodies capable of specifically reacting with the variant products of the invention. Detection of the level of the expression of the variant of the invention in particular as compared to that of the original sequence from which it was varied or compared to other variant sequences all varied from the same original sequence may be indicative of a plurality of physiological or pathological conditions. A preferred example is the detection of ACEV nucleic acid sequence, ACEV product or anti-ACEV antibody.

The method, according to this latter aspect, for detection of a nucleic acid sequence which encodes the variant product in a biological sample, comprises the steps of:

providing a probe comprising at least one of the nucleic acid (a) sequences defined above;

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- contacting the biological sample with said probe under conditions (b) allowing hybridization of nucleic acid sequences thereby enabling formation of hybridization complexes;
- detecting hybridization complexes, wherein the presence of the (c) complexes indicates the presence of nucleic acid sequence encoding the variant product in the biological sample.

The method as described above is qualitative, i.e. indicates whether the transcript is present in or absent from the sample. The method can also be quantitative, by determining the level of hybridization complexes and then

calibrating said levels to determining levels of transcripts of the desired variant in the sample.

Both qualitative and quantitative determination methods can be used for diagnostic, prognostic and therapy planning purposes.

By a preferred embodiment the probe is part of a nucleic acid chip used for detection purposes, i.e. the probe is a part of an array of probes each present in a known location on a solid support.

The nucleic acid sequence used in the above method may be a DNA sequence an RNA sequence, etc; it may be a coding or a sequence or a sequence complementary thereto (for respective detection of RNA transcripts or coding-DNA sequences). By quantization of the level of hybridization complexes and calibrating the quantified results it is possible also to detect the level of the transcript in the sample.

Methods for detecting mutations in the region coding for the variant product are also provided, which may be methods carried-out in a binary fashion, namely merely detecting whether there is any mismatches between the normal variant nucleic acid sequence of the invention and the one present in the sample, or carried-out by specifically detecting the nature and location of the mutation.

The present invention also concerns a method for detecting variant product in a biological sample, comprising the steps of:

- (a) contacting with said biological sample the antibody of the invention, thereby forming an antibody-antigen complex; and
 - (b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of variant product in said biological sample.

Many diseases are diagnosed by detecting the presence of antibodies against a protein characterizing the disease in the blood, serum or any other body fluid of the patient. The present invention also concerns a method for detecting anti-variant antibody in a biological sample, comprising:

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(a) contacting said sample with the variant product of the invention, thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of anti-variant antibody in the sample.

As indicated above, both methods (for detection of variant product and for detection of the anti-variant antibody) can be quantitized to determine the level or the amount of the variant or antibody in the sample, alone or in comparison to the level of the original amino acid sequence from which it was varied or compared to the level of antibodies against the original amino acid sequence, and qualitative and quantitative results may be used for diagnostic, prognostic and therapy planning purposes.

The invention also concerns distinguishing antibodies, i.e. antibodies capable of binding either to the variant product or to the original sequence from which the variant has been varied, while not binding to the original sequence or the variant product respectively. These distinguishing antibodies may be used for detection purposes.

By yet another aspect the invention also provides a method for identifying candidate compounds capable of binding to the variant product and modulating its activity (being either activators or deactivators). The method includes:

- (i) providing a protein or polypeptide comprising an amino acid sequence substantially as depicted in any one of SEQ ID NO: 88 to 174, or a fragment of such a sequence;
 - (ii) contacting a candidate compound with said amino acid sequence;
- (iii) measuring the physiological effect of said candidate compound on the activity of the amino acid sequences and selecting those compounds which show a significant effect on said physiological activity.

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The present invention also concerns compounds identified by the above methods described above, which compound may either be an activator of the variant product or a deactivator thereof.

PCT/IL00/00766 WO 01/36632

BRIEF DESCRIPTION OF THE DRAWINGS

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In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

- Fig. 1 is a comparison between the amino acid sequence of SEQ ID NO: 88 and the original sequence from which it has been varied;
 - Fig. 2 is a comparison between the amino acid sequence of SEQ ID NO: 89 and the original sequence from which it has been varied;
- Fig. 3 is a comparison between the amino acid sequence of SEQ ID NO: 90 and the original sequence from which it has been varied;
 - Fig. 4 is a comparison between the amino acid sequence of SEQ ID NO: 91 and the original sequence from which it has been varied;
 - Fig. 5 is a comparison between the amino acid sequence of SEQ ID NO: 92 and the original sequence from which it has been varied;
 - Fig. 6 is a comparison between the amino acid sequence of SEQ ID NO: 93 and the original sequence from which it has been varied;
 - Fig. 7 is a comparison between the amino acid sequence of SEQ ID NO: 94 and the original sequence from which it has been varied;
 - Fig. 8 is a comparison between the amino acid sequence of SEQ ID NO: 95 and the original sequence from which it has been varied;
 - Fig. 9 is a comparison between the amino acid sequence of SEQ ID NO: 96 and the original sequence from which it has been varied;
 - Fig. 10 is a comparison between the amino acid sequence of SEQ ID NO: 97 and the original sequence from which it has been varied;
- Fig. 11 is a comparison between the amino acid sequence of SEQ ID 25 NO: 98 and the original sequence from which it has been varied;
 - Fig. 12 is a comparison between the amino acid sequence of SEQ ID NO: 99 and the original sequence from which it has been varied;
- Fig. 13 is a comparison between the amino acid sequence of SEQ ID NO: 100 and the original sequence from which it has been varied;

- Fig. 14 is a comparison between the amino acid sequence of SEQ ID NO: 101 and the original sequence from which it has been varied;
- Fig. 15 is a comparison between the amino acid sequence of SEQ ID NO: 102 and the original sequence from which it has been varied;
- Fig. 16 is a comparison between the amino acid sequence of SEQ ID NO: 103 and the original sequence from which it has been varied;

- Fig. 17 is a comparison between the amino acid sequence of SEQ ID NO: 104 and the original sequence from which it has been varied;
- Fig. 18 is a comparison between the amino acid sequence of SEQ ID NO: 105 and the original sequence from which it has been varied;
 - Fig. 19 is a comparison between the amino acid sequence of SEQ ID NO: 106 and the original sequence from which it has been varied;
 - Fig. 20 is a comparison between the amino acid sequence of SEQ ID NO: 107 and the original sequence from which it has been varied;
 - Fig. 21 is a comparison between the amino acid sequence of SEQ ID NO: 108 and the original sequence from which it has been varied;
 - Fig. 22 is a comparison between the amino acid sequence of SEQ ID NO: 109 and the original sequence from which it has been varied;
- Fig. 23 is a comparison between the amino acid sequence of SEQ ID NO: 110 and the original sequence from which it has been varied;
 - Fig. 24 is a comparison between the amino acid sequence of SEQ ID NO: 111 and the original sequence from which it has been varied;
 - Fig. 25 is a comparison between the amino acid sequence of SEQ ID NO: 112 and the original sequence from which it has been varied;
- Fig. 26 is a comparison between the amino acid sequence of SEQ ID 25 NO: 113 and the original sequence from which it has been varied;
 - Fig. 27 is a comparison between the amino acid sequence of SEQ ID NO: 114 and the original sequence from which it has been varied;
- Fig. 28 is a comparison between the amino acid sequence of SEQ ID NO: 115 and the original sequence from which it has been varied;

- Fig. 29 is a comparison between the amino acid sequence of SEQ ID NO: 116 and the original sequence from which it has been varied;
- Fig. 30 is a comparison between the amino acid sequence of SEQ ID NO: 117 and the original sequence from which it has been varied;
- Fig. 31 is a comparison between the amino acid sequence of SEQ ID NO: 118 and the original sequence from which it has been varied;
 - Fig. 32 is a comparison between the amino acid sequence of SEQ ID NO: 119 and the original sequence from which it has been varied;
- Fig. 33 is a comparison between the amino acid sequence of SEQ ID NO: 120 and the original sequence from which it has been varied;
 - Fig. 34 is a comparison between the amino acid sequence of SEQ ID NO: 121 and the original sequence from which it has been varied;
 - Fig. 35 is a comparison between the amino acid sequence of SEQ ID NO: 122 and the original sequence from which it has been varied;
 - Fig. 36 is a comparison between the amino acid sequence of SEQ ID NO: 123 and the original sequence from which it has been varied;
 - Fig. 37 is a comparison between the amino acid sequence of SEQ ID NO: 124 and the original sequence from which it has been varied;
- Fig. 38 is a comparison between the amino acid sequence of SEQ ID NO: 125 and the original sequence from which it has been varied;
 - Fig. 39 is a comparison between the amino acid sequence of SEQ ID NO: 126 and the original sequence from which it has been varied;
 - Fig. 40 is a comparison between the amino acid sequence of SEQ ID NO: 127 and the original sequence from which it has been varied;
- Fig. 41 is a comparison between the amino acid sequence of SEQ ID NO: 128 and the original sequence from which it has been varied;
 - Fig. 42 is a comparison between the amino acid sequence of SEQ ID NO: 129 and the original sequence from which it has been varied;
- Fig. 43 is a comparison between the amino acid sequence of SEQ ID NO: 130 and the original sequence from which it has been varied;

- Fig. 44 is a comparison between the amino acid sequence of SEQ ID NO: 131 and the original sequence from which it has been varied;
- Fig. 45 is a comparison between the amino acid sequence of SEQ ID NO: 132 and the original sequence from which it has been varied;
- Fig. 46 is a comparison between the amino acid sequence of SEQ ID NO: 133 and the original sequence from which it has been varied;
- Fig. 47 is a comparison between the amino acid sequence of SEQ ID NO: 134 and the original sequence from which it has been varied;
- Fig. 48 is a comparison between the amino acid sequence of SEQ ID NO: 135 and the original sequence from which it has been varied;
 - Fig. 49 is a comparison between the amino acid sequence of SEQ ID NO: 136 and the original sequence from which it has been varied;
 - Fig. 50 is a comparison between the amino acid sequence of SEQ ID NO: 137 and the original sequence from which it has been varied;
 - Fig. 51 is a comparison between the amino acid sequence of SEQ ID NO: 138 and the original sequence from which it has been varied;
 - Fig. 52 is a comparison between the amino acid sequence of SEQ ID NO: 139 and the original sequence from which it has been varied;
- Fig. 53 is a comparison between the amino acid sequence of SEQ ID NO: 140 and the original sequence from which it has been varied;
 - Fig. 54 is a comparison between the amino acid sequence of SEQ ID NO: 141 and the original sequence from which it has been varied;
 - Fig. 55 is a comparison between the amino acid sequence of SEQ ID NO: 142 and the original sequence from which it has been varied;
- Fig. 56 is a comparison between the amino acid sequence of SEQ ID NO: 143 and the original sequence from which it has been varied;
 - Fig. 57 is a comparison between the amino acid sequence of SEQ ID NO: 144 and the original sequence from which it has been varied;
- Fig. 58 is a comparison between the amino acid sequence of SEQ ID NO:
 145 and the original sequence from which it has been varied;

- Fig. 59 is a comparison between the amino acid sequence of SEQ ID NO: 146 and the original sequence from which it has been varied;
- Fig. 60 is a comparison between the amino acid sequence of SEQ ID NO: 147 and the original sequence from which it has been varied;
- Fig. 61 is a comparison between the amino acid sequence of SEQ ID NO: 148 and the original sequence from which it has been varied;
- Fig. 62 is a comparison between the amino acid sequence of SEQ ID NO: 149 and the original sequence from which it has been varied;
- Fig. 63 is a comparison between the amino acid sequence of SEQ ID NO:

 150 and the original sequence from which it has been varied;
 - Fig. 64 is a comparison between the amino acid sequence of SEQ ID NO: 151 and the original sequence from which it has been varied;
 - Fig. 65 is a comparison between the amino acid sequence of SEQ ID NO: 152 and the original sequence from which it has been varied;
 - Fig. 66 is a comparison between the amino acid sequence of SEQ ID NO: 153 and the original sequence from which it has been varied;

- Fig. 67 is a comparison between the amino acid sequence of SEQ ID NO: 154 and the original sequence from which it has been varied;
- Fig. 68 is a comparison between the amino acid sequence of SEQ ID NO: 20 155 and the original sequence from which it has been varied;
 - Fig. 69 is a comparison between the amino acid sequence of SEQ ID NO: 156 and the original sequence from which it has been varied;
 - Fig. 70 is a comparison between the amino acid sequence of SEQ ID NO: 157 and the original sequence from which it has been varied;
- Fig. 71 is a comparison between the amino acid sequence of SEQ ID NO: 158 and the original sequence from which it has been varied;
 - Fig. 72 is a comparison between the amino acid sequence of SEQ ID NO: 159 and the original sequence from which it has been varied;
- Fig. 73 is a comparison between the amino acid sequence of SEQ ID NO: 160 and the original sequence from which it has been varied;

- Fig. 74 is a comparison between the amino acid sequence of SEQ ID NO: 161 and the original sequence from which it has been varied;
- Fig. 75 is a comparison between the amino acid sequence of SEQ ID NO: 162 and the original sequence from which it has been varied;
- Fig. 76 is a comparison between the amino acid sequence of SEQ ID NO: 163 and the original sequence from which it has been varied;
 - Fig. 77 is a comparison between the amino acid sequence of SEQ ID NO: 164 and the original sequence from which it has been varied;
- Fig. 78 is a comparison between the amino acid sequence of SEQ ID NO:
 10 165 and the original sequence from which it has been varied;
 - Fig. 79 is a comparison between the amino acid sequence of SEQ ID NO: 166 and the original sequence from which it has been varied;
 - Fig. 80 is a comparison between the amino acid sequence of SEQ ID NO: 167 and the original sequence from which it has been varied;
 - Fig. 81 is a comparison between the amino acid sequence of SEQ ID NO: 168 and the original sequence from which it has been varied;
 - Fig. 82 is a comparison between the amino acid sequence of SEQ ID NO: 169 and the original sequence from which it has been varied;
 - Fig. 83 is a comparison between the amino acid sequence of SEQ ID NO:
 170 and the original sequence from which it has been varied;
 - Fig. 84 is a comparison between the amino acid sequence of SEQ ID NO: 171 and the original sequence from which it has been varied;
 - Fig. 85 is a comparison between the amino acid sequence of SEQ ID NO: 172 and the original sequence from which it has been varied;
- Fig. 86 is a comparison between the amino acid sequence of SEQ ID NO: 173 and the original sequence from which it has been varied;
 - Fig. 87 is a comparison between the amino acid sequence of SEQ ID NO: 174 and the original sequence from which it has been varied;

Fig. 88 shows immunohistochemical staining with antibodies against a fragment of the ACEV product of SEQ ID NO: 144; expressed in ductal epitilus in salivatory gland (magnification X 100);

Fig. 89 shows the same as in Fig. 89 (magnification X 400);

Fig. 90 shows immunohistochemical staining with antibodies against a fragment of ACEV product of SEQ ID NO: 144 expressed in salivary glands surrounding the lymph nodes; and

Fig. 91 shows RT-PCR results of the ACEV sequence expressed in salivary glands.

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DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Example I: Comparison of variants with original sequences

Original sequences were obtained from GenBank Version 110.

Comparison between the original sequences and the novel variant sequences was made using the Pileup application from the GCG suite version 10.0 (January 1999), with the default values:

Gap creation penalty (GapWeight): 8

Gap extension penalty (GapLengthWeight): 2

The comparison is shown in Fig. 1 to 87 which show the comparison of each of the variant products depicted in SEQ ID NO: 88 to 174 with the original sequence from which it was varied.

The following is a list which gives the name and the description of each original sequence from which the alternative splice variant has been varied by alternative splicing. The description is followed by the internal reference to the novel variant (NV-NV... or NV-... etc.) and a short comparison between the variant and the original sequence. It should be noticed that several splice variants may have been originated from the same parent sequence by several different alternative splicings. The following table summarizes the accession number of the original sequence, the terminology of the new variant (RN-NV... or NV-...) and the description of the difference between the new variant and the original sequence.

Table

Accession	SEQ ID NO:	Description of the New Variant
AA2A_HUMAN	88	Gap between amino acids at the positions 237-247 of the original protein. Missing 6th transmembrane loop of the original Adenosine A2 receptor.
ASM_HUMAN	89	Insertion of 2 amino acids after amino acid at the position 34 and insertion of 54 amino acids after amino acid at the position 492 of the original SPHINGOMYELIN PHOSPHODIESTERASE protein.
FA12_HUMAN	90	Alternative 10 C-terminal amino acids. Has part of catalytic domain missing 1 active site.
GCSR_HUMAN	91	Deletion of 62 amino acids between the positions 320-382 of the original GRANULOCYTE COLONY STIMULATING FACTOR receptor. The deletion is in the EXTRACELLULAR domain in one of the FIBRONECTIN TYPE-III domains R1.
GCSR_HUMAN	92	Insertion of 37 amino acids in the extracellular domain after the position 574 of the original GRANULOCYTE COLONY STIMULATING FACTOR receptor.
GLR2_HUMAN	93	Replacement of 88 C-terminal amino acids of the original glutamate receptor 2 by alternative 42 amino acids. Has most of domains, might be missing 4th transmembrane domain.
GLUC_HUMAN	94	Gap; 156aa compared to 180aa; exact 1-108; gap 108-132; exact 132-180. Missing almost whole GLUCAGON-LIKE PEPTIDE 1
IHBA_HUMAN	95	Replacement of 128 N-terminal amino acids of the original inhibin protein by alternative 5 amino acids. The deleted part contains propep and glycosylation site of the original protein. The resulting new variant sustains the inhibin beta chain.
IL6_HUMAN	96	Deletion of 17 amino acids between the positions 79-96 of the original interleukin 6 protein. Has all necessary domains.
IL6_HUMAN	97	Deletion of 55 amino acids between the positions 6-61 of the original protein. Has only the beginning of signal peptide; has disulfide bonds and carbohydrate region.
RELI_HUMAN	98	Insertion of 35 amino acids after the amino acid

een the protein. at the position alternative and. long compared are different. PEATS MINAL, missing
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	105	Dulanment of 10 amine saids between the
TYPH_HUMAN	105	Replacement of 48 amino acids between the
		positions 216-264 of the original protein by
		alternative 9 amino acids.
TYPH_HUMAN	106	Deletion of 119 amino acids between the
		positions 333-452, missing 3 rd repeat of the
		original protein. Replacement of 48 amino
		acids between the positions 216-264 of the
		original protein by alternative 9 amino acids.
IC1 HUMAN	107	Deletion of 19 amino acids between the
		positions 29-48 of the original protein. Missing
•		1 glycosylation out of 14.
PT16 HUMAN	108	Deletion of 261 N-terminal amino acids of the
1110_1101		original protein (the first possible Met is at the
		position 261). The new variant has 116 amino
	ŀ	acids compared to 376 in the original protein
		(exact 261-376), including the active site.
PT16_HUMAN	109	Deletion of 57 amino acids between the
1110_11014114	1,07	positions 267-325 of the original protein. The
		resulting new variant contains the active site.
PT16 HUMAN	110	Deletion of 189 amino acids between the
FIIO_HOMAN	110	positions 89-278 of the original protein. The
		resulting new variant contains the active site.
DT16 LITIMANI	111	Replacement of 376 C-terminal amino acids of
PT16_HUMAN	111	the original protein by alternative 5 amino
		acids. The resulting new variant doesn't contain
		the active site.
TADO ITIMANI	112	Truncated: 305 amino acids compared to 618
IAP2_HUMAN	112	aa (protein 2). The new variant contains exact
·		positions 1-299, last 6 amino acids are
		different. Two SNIPs in position 235 and 241
		of the original protein. The new variant is
		missing Zn Finger and half of 3 rd BIR repeat.
CET IIII) (A)I	113	Extra 83 amino acids in the N-terminus of the
SET_HUMAN	113	protein. The added sequence has predicted
		potential transmembrane domain (probable
		signal peptide?)
OPER THUNGARD	114	Replacement of 24 C-terminal amino acids of
SET_HUMAN	114	the original protein by alternative 8 amino
		acids. Missing part of ASP/GLU-RICH and
		BREAKPOINT FOR TRANSLOCATION TO
		FORM SET-CAN ONCOGENE.
	115	Deletion of 178 amino acids at the positions
CDNC_HUMAN	115	97-275 of the original protein. Insertion of 121
		9/-2/5 of the original protein. The resulting
	· {	amino acids at the N-terminus. The resulting
		new variant is missing PAPA repeats.
F13B_MOUSE	116	Deletion of 87 C-terminal amino acids of the
		original protein. SNIP at position 236 (L->V).
		The resulting new variant is missing the last

		shushi repeat. Deletion of 641 amino acids between the
EGF_MOUSE	117	Deletion of 641 amino acids between the
_		positions 67-708 of the original protein.
		Missing 4 EGF-like domains, 2 glycosylations,
		9 diSulfide bonds.
EGF_MOUSE	118	Deletion of 641 amino acids between the
		positions 67-708, and deletion of 45 amino
		acids between the positions 1020-1065 of the
		original protein. Missing 4 EGF-like domains,
		2 glycosylations, 9 diSulfide bonds. Missing
		transmembrane domain.
EGF MOUSE	119	Deletion of 641 amino acids between the
EQL_MOOSE	**>	positions 67-708 of the original protein.
İ		Missing 4 EGF-like domains, 2 glycosylations,
		9 diSulfide bonds. Replacement of 419
		C-terminal amino acids by 5 amino acids.
TOTAL MOLICE	120	Deletion of 841 amino acids between the
EGF_MOUSE	120	positions 18-859 of the original protein.
		Missing 5 EGF-like domains and 2
		glycosylation sites.
		Deletion of 774 amino acids between the
EGF_MOUSE	121	positions 5-779 of the original protein. Missing
•		signal peptide, 5 EGF-like domains, and 2
		signal peptide, 5 Doi into dominary
	<u> </u>	glycosylation sites. Deletion of 336 N-terminal amino acids of the
P53_MOUSE	122	original protein. Missing ASP/GLU-RICH
		original protein. Wissing ASI70DO 14011
		(ACIDIC), missing hydrophobic domain,
		missing NUCLEAR LOCALIZATION
		SIGNAL, missing 1 out of 2
		PHOSPHORYLATION sites.
NME3_HUMAN	123	Deletion of 381 N-terminal amino acids of the
_	1	original protein. Missing 2 out of 4
		glycosylation sites.
TRFE_HUMAN	124	Deletion of 34 amino acids between the
_		positions 654-689 of the original protein. Loss
		of disulfide bond.
TRFE_HUMAN	125	Deletion of 52 amino acids between the
114 2		positions 447-499 of the original protein. Loss
		of disulfide bond.
BAA23795	126	Replacement of 83 C-terminal amino acids
I RAA/1/97		from probable cytoplasmic domain of the
BAAZ3/33	l	
BAA23193		original protein by alternative 4 amino acids.
BAAZ3173		original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787
BAAZ3173		original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787
BAAZ3/73		original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787 compared to 4866, exact 1-4783 with last 4
	127	original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787 compared to 4866, exact 1-4783 with last 4 amino acids different. Replacement of 64 C-terminal amino acids of
VIPS_HUMAN	127	original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787 compared to 4866, exact 1-4783 with last 4

		last transmembrane and the cytoplasmic
		domains.
PACR HUMAN	128	Deletion of 22 amino acids between the
FACK_HOWAN	120	positions 88-110 of the original protein The
		deletion is an extracellular loop.
AND THE TAXABLE	129	Deletion of 540 C-terminal amino acids of the
NRP_HUMAN	129	original protein, resulting in truncated new
		variant (383 compared to 923 amino acids).
		The new variant is missing part of the
		extracellular domain, the cytoplasmic and the
		extracellular dollarit, the cytopiasine and are
		transmembrane domains.
NRP_HUMAN	130	Replacement of 595 C-terminal amino acids of
-		the original protein by alternative 11 amino
		acids. The resulting new variant is truncated
		(339 compared to 923 amino acids, exact 1-328
		with last 11 amino acids different), and is
		missing part of the extracellular domain, the
		cytoplasmic and the transmembrane domains.
-:11900200	131	Deletion of 114 amino acids between the
gi 1899200		positions 1257-1372 of the original
		N-METHYL D-ASPARTATE RECEPTOR
		SUBTYPE 2A protein.
	120	Replacement of 56 C-terminal amino acids from
VIPS_HUMAN	132	the cytoplasmic domain of the original protein
		by alternative 73 amino acids.
		Replacement of 56 C-terminal amino acids from
VIPS_HUMAN	133	the cytoplasmic domain of the original protein
		the cytopiasmic domain of the original proton
·		by alternative 70 amino acids.
IG1R HUMAN	134	Deletion of 22 amino acids between the
_		positions 1268-1291 of the original protein. The
		deleted fragment is part of the cytoplasmic
		domain of INSULIN-LIKE GROWTH
	_	FACTOR I RECEPTOR, BETA-CHAIN.
NRP_HUMAN	135	Replacement of 282 C-terminal amino acids of
1114 _11011		the original protein, including the
		transmembrane domain and the MAM domain,
		by alternative 3 amino acids.
NRP_HUMAN	136	Deletion of 83 amino acids between the
MKL_HOMETA	150	positions 538-622 of the original protein. The
		deleted region includes part of the F5/8 TYPE C
		2 domain and part of the MAM domain.
	127	Deletion of 385 C-terminal amino acids of the
NRP_HUMAN	137	original protein, including the transmembrane
		domain and the MAM domain.
		Replacement of 496 C-terminal amino acids of
FGR3_HUMAN	138	the original protein by alternative 79 amino
		the original protein by alternative // annito
		acids The deleted region includes the
		C-terminal part of the extracellular domain, the

		transmembrane domain, the cytoplasmic domain, the protein kinase domain and the two ATP binding domains.
F13B_MOUSE	139	Replacement of 340 aa of the c-terminus of the original protein in 3aa deletion of sushi 6-10 domain
EGF_MOUSE	140	Deletion of 144 amino acids between the positions 1020-1165, including the transmembrane domain and part of the cytoplasmic domain of the original protein.
EGF_MOUSE	141	Replacement of 418 C-terminal amino acids of the original protein by alternative 5 amino acids. The deleted region includes the EGF active chain, 4 out of 9 EGF-like domains within the extracellular region of the protein, the transmembrane and the cytoplasmic regions.
EGF_MOUSE	142	Deletion of 641 amino acids between the positions 66-707 of the original protein. The deleted region is in the extracellular part of the protein and it includes 4 out of 9 EGF-like domains. NV-20 contains the original signal peptide, part of the extracellular domain, the epidermal growth factor chain (located between the positions 977-1029 of the original protein), and the original transmembrane and the cytoplasmic domains.
EGF_MOUSE	143	Deletion of 842 amino acids between the positions 17-859 of the original protein (including replacement of the amino acid in the position 859 by an alternative one). The deleted region is in the extracellular part of the protein and it includes 5 out of 9 EGF-like domains. NV-20 contains the original signal peptide, part of the extracellular domain, the epidermal growth factor chain (located between the positions 977-1029 of the original protein), and the original transmembrane and the cytoplasmic domains.
ACE_MOUSE	144	Replacement of 77 C-terminal amino acids of the original protein, including the entire transmembrane and cytoplasmic domains, by alternative 14 amino acids.
ESR1_MOUSE	145	Replacement of 229 C-terminal amino acids o the original protein, including part of the steroid-binding domain, by alternative 12 amino acids.
FA7_MOUSE	146	Deletion of 101 amino acids, between the positions 119-220 of the original protein. The

		deleted region contains 74 amino acids from the
		C-terminal end of the factor VII light chain, and
!		26 amino acids from the N-terminal end of the
		factor VII heavy catalytic chain. The deleted
		region includes EGF-like 2 domain and the
		cleavage site (by factor XA, factor XIIA, factor
		IXA, or thrombin) of the original protein.
CALL DA LOTTOR	147	Deletion of 33 amino acids, spanning the
CAL0_MOUSE	147	positions 18-50, between the signal and the
		positions 16-30, between the signal and the
	,	calcitonin peptide in the original precursor
		protein.
Gi 2826776	148	Replacement of the last 7 C-terminal amino
•		acids of the original protein by alternative 11
		amino acids.
PTI6_HUMAN	149	Replacement of the last 4 C-terminal amino
		acids of the original protein by alternative 28
		amino acids.
PTI6_HUMAN	150	Replacement of the last 16 C-terminal amino
		acids of the original protein by alternative 12
		amino acids.
_RIN1_HUMAN	151	Replacement of 158 last C-terminal amino acids
		of the original protein by alternative 71 amino
		acids with probable transmembrane region.
CDNC_HUMAN	152	Addition of 121 amino acids at the N-terminus
		of the protein.
CDN2_HUMAN	153	Replacement of 5 amino acids at the positions
		18, 24, 27, 30, 37 of the original protein by
		alternative amino acids. Replacement of last 4
		C-terminal amino acids of the original protein
		by alternative 20 amino acids.
CDN5_HUMAN	154	Replacement of the last 6 C-terminal amino
		acids of the original protein by alternative 52
		amino acids.
HEP2_HUMAN	155	Deletion of 150 amino acids, between the
		positions 334-485, of the original protein. The
		deleted region includes the reactive bond (the
		active site) of the original protein. NV-33 does
		contain the chemotactic activity domain, the
		glycosaminoglycan-binding site and the
		hirudin-like 2 x 11 AA approximate repeats,
		Asp/Glu rich.
TFP2_HUMAN	156	Replacement of 36 C-terminal amino acids of
	1	the original protein by alternative 12 amino
		acids. The deleted region includes part of the
		BPTI/KUNITZ inhibitor domain-3 and the
		poly-Lysine domain of the original protein.
TFP2_HUMAN	157	Deletion of 25 amino acids, between the
	1	positions 153-178 of the original protein, and

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		replacement of the amino acid at the position 179 by alternative one. The deleted region
		includes the active site and part of the
		BPTI/KUNITZ inhibitor domain-3.
TEDI ITIMAN	158	Replacement of 95 C-terminal amino acids of
TFPI_HUMAN	150	the original protein, containing the entire
		BPTI/KUNITZ inhibitor-3 domain, by
,	•	aternative 16 amino acids.
IC1 HUMAN	159	Insertion of 136 aa at position 227 of the
ICI_IIOIvii IIV	1,00	original protein.
PTI6_HUMAN	160	Replacement of last 15 aa in the original
LIIO_IIOMM	100	protein in 28 aa, the cds of the NV has no stop
		codon.
DTIC ITIMANI	161	Replacement of last 185 aa of the original
PTI6_HUMAN	101	protein in 13 aa. The NV lacks the ACT site.
DOTA TITINANI	162	Replacement of last 230 aa of the original
PTI6_HUMAN	102	protein in 10 aa. The NV lacks the ACT site.
CONTRACTOR OF THE CONTRACTOR O	163	Insertion of 35 aa at position 387 of the
TYPH_HUMAN	103	original protein.
CONTO THE MAN	164	Replacement of 220 aa of the c-terminus of
CDNC_HUMAN	104	the original protein in 47 aa. Deletion of all 9
		x 4 aa repeats of p-a-p-a. Deletion of the
		potential nuclear localization signal (278-281
		in the original protein).
	165	Replacement of 264 aa of the c-terminus of
FGR3_HUMAN	165	the original protein in 19 aa. Deletion of part
		of the potential cytoplasmatic protein
		(397-806 in the original protein), part of the
		protein kinase domain (472-761), deletion of
		the ACT site (617).
THE THE CANE	166	Replacement of 58 aa of the c-terminus of the
TFP2_HUMAN	100	original protein in 12 aa. Deletion of part of
		the bpti/kunitz inhibitor 3 domain (158 –208
		in the original protein).
		III the original proteins.
	167	Insertion of 32 aa at position 366 of the
TRFE_HUMAN	167	original protein.
	1.60	Replacement of 388 aa of the c-terminus of
VIPS_HUMAN	168	the original protein in 27 aa. Deletion of all
		potential 7 trans membrena domain.
		Replacement of 180 aa of the n-terminus of
TFPI_HUMAN	169	the original protein in 37 aa. Deletion of the
	1	signal peptide and deletion of the bpti/kunitz
ľ	1	signal peptide and 2 domains
		inhibitor 1 and 2 domains. Replacement of 246 aa of the n-terminus of
P53 MOUSE	170	Replacement of 240 aa of the n-terminas of

		the original protein in 13 aa. Deletion of the asp/glu-rich (acidic) domain.
P53_MOUSE	171	Replacement of 246 aa of the n-terminus of the original protein in 13 aa. Deletion of the asp/glu-rich (acidic) domain.
ACE_MOUSE	172	Replacement of 77 aa of the c-terminus of the original protein in 17 aa. Deletion of the entire transmembrane and cytoplasmatic domains.
ESR1_MOUSE	173	Deletion of 225 aa of the c-terminus of the original protein. Deletion of most of the steroid binding domain (315-599 in the original protein). RT-PCR results implies that the NV exhibits similarity to thr somatic ACE (results not shown).
vesicular GABA and glycine transporter (mouse), gi 2826776	174	Replacement of 73 aa of the c-terminus of the original protein in 21 aa.

Identification of the original sequence from which the novel Variant was variant

The following is the explanation of the definition to be used in the following:

Accession:

Accession number of the original sequence in the GeneBank

.

Name:

Name of the original sequence in the database

Function:

Physiological activity.

SEQ ID NO: Sequence number of variant

database

Description:

10

the difference between the variant and the original sequence.

Accession:

AA2A_HUMAN

Name:

Adenosine A2 receptor

20 Function:

Receptor for adenosine.

SEQ ID 1

Description: Gap between amino acids at the positions 237-247 of the original protein. Missing 6th transmembrane loop of the original Adenosine A2 receptor.

5 Accession:

ASM HUMAN

Name:

SPHINGOMYELIN PHOSPHODIESTERASE

Function:

Converts sphingomyelin to ceramide.

SEQ ID: 2

10

Description: Insertion of 2 amino acids after amino acid at the position 34 and insertion of 54 amino acids after amino acid at the position 492 of the original SPHINGOMYELIN PHOSPHODIESTERASE protein.

15 Accession:

FA12_HUMAN

Name:

COAGULATION FACTOR XII

Function:

Factor XII is a serum glycoprotein that participates in the

initiation of blood coagulation, fibrinolysis, and the

generation of bradykinin and angiotensin.

20

SEQ ID: 3

Description:

Alternative 10 C-terminal amino acids. Has part of catalytic

domain missing 1 active site.

25

30

Accession:

GCSR_HUMAN

Name:

GRANULOCYTE COLONY STIMULATING FACTOR

receptor

Function:

Receptor for granulocyte colony-stimulating factor (g- csf).

In addition it may function in some adhesion or recognition

events at the cell surface.

SEQ ID: 4

Description: Deletion of 62amino acids between the positions 320-382 of the original GRANULOCYTE COLONY STIMULATING FACTOR receptor.

The deletion is in the EXTRACELLULAR domain in one of the FIBRONECTIN TYPE-III domains R1.

Accession:

GCSR_HUMAN

5 Name:

GRANULOCYTE COLONY STIMULATING FACTOR

receptor

Function:

Receptor for granulocyte colony-stimulating factor (g- csf).

In addition it may function in some adhesion or recognition

events at the cell surface.

10

SEQ ID: 5

Description: Insertion of 37 amino acids in the extracellular domain after the position 574 of the original GRANULOCYTE COLONY STIMULATING FACTOR receptor.

Accession:

GLR2 HUMAN

Name:

Glutamate receptor 2

Function:

L-glutamate acts as an excitatory neurotransmitter at many

synapses in the central nervous system. the postsynaptic

actions of Glu are mediated by a variety of receptors are

named according to their selective agonists

SEQ ID: 6

25

20

Description: Replacement of 88 C-terminal amino acids of the original glutamate receptor 2 by alternative 42 amino acids. Has most of domains, might be missing 4th transmembrane domain.

30 Accession:

GLUC_HUMAN

Name:

Glucagon

Function:

Promotes hydrolysis of glycogen and lipids, and raises the

blood sugar level.

35 **SEQ ID:** 7

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- 39 -

Description Gap; 156aa compared to 180aa; exact 1-108; gap 108-132; exact 132-180. Missing almost whole GLUCAGON-LIKE PEPTIDE 1

Accession:

IHBA HUMAN

5 Name:

Inhibin; erythroid differentiation factor

Function:

Inhibin is a gonadal glycopeptide that inhibits the secretion

of follitropin by the pituitary gland. On the other hand activin

activates the secretion of follitropin. Activin is also

important in embryonic axial development.

10

SEQ ID: 8

Description: Replacement of 128 N-terminal amino acids of the original inhibin protein by alternative 5 amino acids. The deleted part contains propep and glycosylation site of the original protein. The resulting new variant sustains the inhibin beta chain.

Accession:

IL6_HUMAN

Name:

Interleukin 6

20 Function:

IL-6 is a cytokine with a wide variety of biological functions: it plays an essential role in the final differentiation

of B-cells into Ig-secreting cells, it induces myeloma and plasmacytoma growth, it induces nerve cells differentiation.

25 **SEQ ID:9**

Description: Deletion of 17 amino acids between the positions 79-96 of the original interleukin 6 protein. Has all necessary domains.

30 Accession:

IL6_HUMAN

Name:

Interleukin 6

Function:

IL-6 is a cytokine with a wide variety of biological

functions: it plays an essential role in the final differentiation of B-cells into Ig-secreting cells, it induces myeloma

and plasmacytoma growth, it induces nerve cells

differentiation.

35

Description: Deletion of 55 amino acids between the positions 6-61 of the original protein. Has only the beginning of signal peptide; has disulfide bonds and carbohydrate region.

Accession:

RELI HUMAN

Name:

Relaxin

Function:

Relaxin is an ovarian hormone that acts with estrogen to

produce dilatation of the birth canal in many mammals.

SEQ ID: 11

Description: Insertion of 35 amino acids after the amino acid at the position 70 of the original relaxin protein. The insertion is in the connecting peptide.

Accession:

SY04_HUMAN

Name:

SMALL INDUCIBLE CYTOKINE A4, MACROPHAGE

INFLAMMATORY PROTEIN 1-BETA

20 Function:

Monokine with inflammatory and chemokinetic properties

SEQ ID: 12

Description: Deletion of 5 amino acids between the positions 65-69 of the original protein. Replacement of the amino acid at the position 70 of the original protein by an alternative amino acid. Missing part of strand.

Accession:

TSP1 HUMAN

Name:

Thrombospondin adhesive glycoprotein

30 Function:

Adhesive glycoprotein that mediates cell-to-cell and

cell-to-matrix interactions. Can bind to fibrinogen,

fibronectin, laminin and type v collagen

SEQ ID: 13

35

Description: Truncated exact 1-722 (731aa long compared to 1170aa), last 9 amino acids are different. Missing 7 X TSP TYPE-3 REPEATS CA-BINDING

domain C-TERMINAL, missing CELL ATTACHMENT SITE, missing 1 out of 4 glycosylation sites. Has all other components including signal peptide

Accession:

TSP1_HUMAN

5 Name:

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Thrombospondin adhesive glycoprotein

Function: Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Can bind to fibrinogen, fibronectin, laminin and type v collagen

SEQ ID: 14

Description: Truncated exact 1-548 (555aa long compared to 1170) last 7aa different. Missing 3 X EGF-TYPE REPEATS, missing 7 X TSP TYPE-3 REPEATS Ca-BINDING domain C-TERMINAL missing CELL ATTACHMENT SITE, missing all diSulfide bonds, missing 2 out of 4 glycosylation sites. Has all other domains (including signal peptide).

Accession:

TSP1 HUMAN

Name:

Thrombospondin adhesive glycoprotein

on Function:

Adhesive glycoprotein that mediates cell-to-cell and

cell-to-matrix interactions. Can bind to fibrinogen,

fibronectin, laminin and type v collagen

SEQ ID: 15

25 -

Description: Truncated exact 1-490 (546aa long compared to 1170) last 56 amino acids are different. Missing 1 out of 3 X TSP TYPE-1 REPEATS (CS-LIKE), Missing 3 X EGF-TYPE REPEATS, missing 7 X TSP TYPE-3 REPEATS CA-BINDING domain C-TERMINAL missing CELL ATTACHMENT SITE, missing all diSulfide bonds, missing 2 out of 4 glycosylations. Has all other domains (including signal peptide).

Accession:

TSP1 HUMAN

Name:

Thrombospondin adhesive glycoprotein

35 Function

Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Can bind to fibrinogen,

fibronectin, laminin and type v collagen

Description: Truncated: exact 1-431aa (459aa long compared to 1170) last 28 amino acids are different. Missing 2 out of 3 X TSP TYPE-1 REPEATS (CS-LIKE), Missing 3 X EGF-TYPE REPEATS, missing 7 X TSP TYPE-3 REPEATS CA-BINDING domain C-TERMINAL missing CELL ATTACHMENT SITE, missing all diSulfide bonds, missing 2 out of 4 glycosylations. Has all other domains (including signal peptide).

10

Accession:

TYPH HUMAN

Name:

PLATELET-DERIVED ENDOTHELIAL CELL GROWTH

FACTOR

Function:

May have a role in maintaining the integrity of the blood vessels. Has growth promoting activity on endothelial cells, angiogenic activity in vivo and chemotactic activity on

endothelial cells in vitro.

20

15

CATALYSES THE REVERSIBLE PHOSPHOROLYSIS OF THYMIDINE. THE PRODUCED MOLECULES ARE THEN UTILIZED AS CARBON AND ENERGY SOURCES OR IN THE RESCUE OF PYRIMIDINE

BASES FOR NUCLEOTIDE SYNTHESIS.

SIMILARITY: BELONGS TO THYMIDINE/ PYRIMIDINE-NUCLEOSIDE PHOSPHORYLASES

25

FAMILY.

SEQ ID: 17

Description: Deletion of 119 amino acids between the positions 333-452 of the original protein. The resulting new variant is missing the 3rd repeat of the original protein.

Accession:

TYPH HUMAN

35 **Name**:

PLATELET-DERIVED ENDOTHELIAL CELL GROWTH

FACTOR

Function:

May have a role in maintaining the integrity of the vessels. Has growth promoting activity on endothelial cells, angiogenic activity in vivo and chemotactic activity on endothelial cells *in vitro*.

5

CATALYSES THE REVERSIBLE PHOSPHOROLYSIS OF THYMIDINE. THE PRODUCED MOLECULES ARE THEN UTILIZED AS CARBON AND ENERGY SOURCES OR IN THE RESCUE OF PYRIMIDINE BASES FOR NUCLEOTIDE SYNTHESIS.

10

SIMILARITY: BELONGS TO THYMIDINE/ PYRIMIDINE-NUCLEOSIDE PHOSPHORYLASES FAMILY.

SEQ ID: 18

15

Description: Replacement of 48 amino acids between the positions 216-264 of the original protein by alternative 9 amino acids.

Accession:

TYPH HUMAN

20 Name:

PLATELET-DERIVED ENDOTHELIAL CELL GROWTH

FACTOR

Function:

May have a role in maintaining the integrity of the vessels. Has growth promoting activity on endothelial cells, angiogenic activity in vivo and chemotactic activity on endothelial cells in vitro.

25

CATALYSES THE REVERSIBLE PHOSPHOROLYSIS OF THYMIDINE. THE PRODUCED MOLECULES ARE THEN UTILIZED AS CARBON AND ENERGY SOURCES OR IN THE RESCUE OF PYRIMIDINE BASES FOR NUCLEOTIDE SYNTHESIS.

30

SIMILARITY: BELONGS TO THYMIDINE/ PYRIMIDINE-NUCLEOSIDE PHOSPHORYLASES

FAMILY.

Description: Deletion of 119 amino acids between the positions 333-452, missing 3rd repeat of the original protein. Replacement of 48 amino acids between the positions 216-264 of the original protein by alternative 9 amino acids.

Accession:

IC1_HUMAN

Name:

PLASMA PROTEASE C1 INHIBITOR

10 Function:

15

20

Activation of the c1 complex is under control of the c1-. Inhibitor. IT FORMS A PROTEOLYTICALLY INACTIVE

STOICHIOMETRIC COMPLEX WITH THE C1R OR C1S PROTEASES. MAY PLAY A POTENTIALLY CRUCIAL

ROLE IN REGULATING IMPORTANT

PHYSIOLOGICAL PATHWAYS INCLUDING COMPLEMENT ACTIVATION, BLOOD

COAGULATION, FIBRINOLYSIS AND THE

GENERATION OF KININS.

PTM: HIGHLY GLYCOSYLATED (49%).

SIMILARITY: BELONGS TO THE SERPIN FAMILY.

SEQ ID NO: 20

Description: Deletion of 19 amino acids between the positions 29-48 of the original protein. Missing 1 glycosylation out of 14.

Accession:

PTI6 HUMAN

Name:

PLACENTAL THROMBIN INHIBITOR

Function:

Cytoplasmic antiproteinase.

30

SIMILARITY: BELONGS TO THE SERPIN FAMILY.

OV-SERPIN SUBFAMILY.

SEQ ID: 21

Description: Deletion of 261 N-terminal amino acids of the original protein (the first possible Met is at the position 261). The new variant has 116 amino

acids compared to 376 in the original protein (exact 261-376), including the active site.

Accession:

PTI6 HUMAN

Name:

PLACENTAL THROMBIN INHIBITOR

5 Function:

Cytoplasmic antiproteinase

SIMILARITY: BELONGS TO THE SERPIN FAMILY.

OV-SERPIN SUBFAMILY.

SEQ ID: 22

10

Description: Deletion of 57 amino acids between the positions 267-325 of

the original protein. The resulting new variant contains the active site.

Accession:

PTI6 HUMAN

Name:

PLACENTAL THROMBIN INHIBITOR

5 Function:

Cytoplasmic antiproteinase

SEQ ID: 23

Description: Deletion of 189 amino acids between the positions 89-278 of the original protein. The resulting new variant contains the active site.

Accession:

PTI6 HUMAN

Name:

PLACENTAL THROMBIN INHIBITOR

Function:

Cytoplasmic antiproteinase

25

SEQ ID: 24

Description: Replacement of 376 C-terminal amino acids of the original protein by alternative 5 amino acids. The resulting new variant doesn't contain the active site.

Accession:

IAP2 HUMAN

Name:

INHIBITOR OF APOPTOSIS PROTEIN 2

Function:

Apoptotic suppressor. The BIR motifs region interacts with

TNF receptor associated factors 1 and 2 (traf1 and traf2) to

form an heteromeric complex, which is then recruited to the

tumor necrosis factor receptor 2 (TNFR2).

Description: Truncated: 305 amino acids compared to 618 aa(protein 2). The 5 new variant contains exact positions 1-299, last 6 amino acids are different. Two SNIPs in positions 235 and 241 of the original protein. The new variant is missing Zn Finger and half of 3rd BIR repeat.

Accession:

SET HUMAN

10 Name:

PHOSPHATASE 2A INHIBITOR 12PP2A

Function:

May be involved in the generation of intracellular signaling events that lead to regulation of transcriptional activity after binding of a ligand to HLA class II molecules. Potent

inhibitor of protein phosphatase 2a.

15

SEQ ID: 26

Description: Extra 83 amino acids in the N-terminus of the protein. The added sequence has predicted potential transmembrane domain (probable signal 20 peptide?)

Accession:

SET HUMAN

Name:

PHOSPHATASE 2A INHIBITOR I2PP2A

Function:

May be involved in the generation of intracellular signaling

events that lead to regulation of transcriptional activity after

binding of a ligand to HLA class II molecules. Potent

inhibitor of protein phosphatase 2a.

SEQ ID: 27

30

25

Replacement of 24 C-terminal amino acids of the original **Description**: protein by alternative 8 amino acids. Missing part of ASP/GLU-RICH and **BREAKPOINT FOR TRANSLOCATION** TO **FORM SET-CAN** ONCOGENE.

35

Accession:

CDNC HUMAN

Name:

CYCLIN-DEPENDENT KINASE INHIBITOR 1C

Function:

5

10

POTENT TIGHT-BINDING INHIBITOR OF SEVERAL G1 CYCLIN/CDK COMPLEXES (CYCLIN E-CDK2, CYCLIN D2-CDK4, AND CYCLIN A-CDK2) AND, TO LESSER EXTENT, OF THE MITOTIC CYCLIN B-CDC2. NEGATIVE REGULATOR OF CELL PROLIFERATION. MAY PLAY A ROLE IN MAINTENANCE OF THE NONPROLIFERATIVE STATE THROUGHOUT LIFE. SUBCELLULAR

LOCATION:

NUCLEAR

(BY

SIMILARITY).

DISEASE: CDKN1C MUTATIONS ARE INVOLVED IN

TUMOR FORMATION.

SEQ ID: 28

Deletion of 178 amino acids at the positions 97-275 of the Description: original protein. Insertion of 121 amino acids at the N-terminus. The resulting new variant is missing PAPA repeats.

Accession:

F13B MOUSE

20 Name:

COAGULATION FACTOR XIII B CHAIN.

Function:

The B chain of factor XIII is not catalytically active, but is thought to stabilize the a subunits and regulate the rate of

transglutaminase formation by thrombin

25 **SEQ ID: 29**

Description

Deletion of 87 C-terminal amino acids of the original protein. SNIP at position 236 (L->V). The resulting new variant is missing the last shushi repeat.

30

Accession:

EGF MOUSE

Name:

PRO-EPIDERMAL GROWTH FACTOR

Function:

Stimulates the growth of various epidermal and epithelial

tissues.

35

SEQ ID: 30

Description: Deletion of 641 amino acids between the positions 67-708 of the original protein. Missing 4 EGF-like domains, 2 glycosylations, 9 diSulfide bonds.

5 Accession:

EGF_MOUSE

Name:

PRO-EPIDERMAL GROWTH FACTOR

Function:

Stimulates the growth of various epidermal and epithelial

Tissues

Description: Deletion of 641 amino acids between the positions 67-708, and deletion of 45 amino acids between the positions 1020-1065 of the original protein. Missing 4 EGF-like domains, 2 glycosylations, 9diSulfide bonds. Missing transmembrane domain.

Accession:

EGF_MOUSE

Name:

PRO-EPIDERMAL GROWTH FACTOR

10 Function:

Stimulates the growth of various epidermal and epithelial

tissues

SEQ ID: 32

15 Description:

Deletion of 641 amino acids between the positions 67-708 of the original protein. Missing 4 EGF-like domains, 2 glycosylations, 9 diSulfide bonds. Replacement of 419 C-terminal amino acids by 5 amino acids.

20 Accession:

EGF MOUSE

Name:

PRO-EPIDERMAL GROWTH FACTOR

Function:

Stimulates the growth of various epidermal and epithelial

Tissues

25 SEQ ID: 33

Description: Deletion of 841 amino acids between the positions 18-859 of the original protein. Missing 5 EGF-like domains and 2 glycosylation sites.

30 Accession:

EGF_MOUSE

Name:

PRO-EPIDERMAL GROWTH FACTOR

Function:

Stimulates the growth of various epidermal and epithelial

Tissues

Description: Deletion of 774 amino acids between the positions 5-779 of the original protein. Missing signal peptide, 5 EGF-like domains, and 2 glycosylation sites.

Accession:

P53_MOUSE

Name:

CELLULAR TUMOR ANTIGEN P53

Function:

Acts as a tumor suppressor in many tumor types. Induces growth arrest or apoptosis depending on the physiological

circumstances or cell type, but both activities are involved in

tumor suppression.

SEQ ID: 35

15

10

Description: Deletion of 336 N-terminal amino acids of the original protein. Missing ASP/GLU-RICH (ACIDIC), missing hydrophobic domain, missing NUCLEAR LOCALIZATION SIGNAL, missing 1 out of 2 PHOSPHORYLATION sites.

20

Accession:

NME3 HUMAN

Name:

GLUTAMATE

[NMDA] RECEPTOR

SUBUNIT

EPSILON 3

Function:

NMDA receptor subtype of glutamate-gated ion channels

25

possesses high calcium permeability and voltage-dependent

sensitivity to magnesium and is mediated by glycine.

SEQ ID: 36

Description: Deletion of 381 N-terminal amino acids of the original protein.

Missing 2 out of 4 glycosylation sites.

Accession:

TRFE HUMAN

Name:

SEROTRANSFERRIN

35 Function:

Iron binding transport proteins

Deletion of 34 amino acids between the positions 654-689 of the **Description:** original protein. Loss of disulfide bond.

5

Accession:

TRFE HUMAN

Name:

SEROTRANSFERRIN

Function:

Iron binding transport proteins

SEQ ID: 38

Deletion of 52 amino acids between the positions 447-499 of the Description: original protein. Loss of disulfide bond.

15 Accession:

BAA23795

Name:

Brain ryanodine receptor

SEQ ID: 39

- 20

Replacement of 83 C-terminal amino acids from probable Description: cytoplasmic domain of the original protein by alternative 4 amino acids. Resulting in truncated new variant: 4787 compared to 4866, exact 1-4783 with last 4 amino acids different.

25

30

Accession:

VIPS HUMAN

Name:

VASOACTIVE

INTESTINAL

POLYPEPTIDE

RECEPTOR 2

Function:

This is a receptor for VIP as well as PACAP-38 and -27, the activity of this receptor is mediated by G proteins which cyclase. adenylyl

activate

Can be coupled

phospholipase C.

SEQ ID: 40

Replacement of 64 C-terminal amino acids of the original Description: protein by alternative 7 amino acids. The resulting new variant is missing the last transmembrane and the cytoplasmic domains.

Accession:

PACR HUMAN

Name:

5

PITUITARY ADENYLATE CYCLASE ACTIVATING

POLYPEPTIDE TYPE RECEPTOR

Function:

This is a receptor for PACAP-27 and PACAP-38. The activity of this receptor is mediated by G proteins which activate adenylyl cyclase. May regulate the release of

adrenocorticotropin, luteinizing hormone, growth hormone,

prolactin, epinephrine.

10 SEQ ID: 41

Description: Deletion of 22 amino acids between the positions 88-110 of the original protein. The deletion is in extracellular loop.

15 Accession:

NRP HUMAN

Name:

20

NEUROPILIN VASCULAR ENDOTHELIAL CELL

GROWTH FACTOR 165 RECEPTOR

Function:

Calcium-independent cell adhesion molecule that function

during the formation of certain neuronal circuits. Binds to

semaphorin III and to the VEGF165 isoform of VEGF

SEQ ID: 42

Description: Deletion of 540 C-terminal amino acids of the original protein, resulting in truncated new variant (383 compared to 923 amino acids).

The new variant is missing part of the extracellular domain, the cytoplasmic and the transmembrane domains.

Accession:

NRP HUMAN

30 Name:

NEUROPILIN VASCULAR ENDOTHELIAL CELL

GROWTH FACTOR 165 RECEPTOR

Function:

Calcium-independent cell adhesion molecule that during the

formation of certain neuronal circuits. Binds to semaphorin

III and to the VEGF165 isoform of VEGF

R2 NV43

Description: Replacement of 595 C-terminal amino acids of the original protein by alternative 11 amino acids. The resulting new variant is truncated (339 compared to 923 amino acids, exact 1-328 with last 11 amino acids different), and is missing part of the extracellular domain, the cytoplasmic and the transmembrane domains.

Accession:

gi|1899200

10 Name:

15

N-METHYL D-ASPARTATE RECEPTOR SUBTYPE 2A

Function:

NMDA RECEPTOR SUBTYPE OF GLUTAMATE-GATED ION CHANNELS POSSESSES HIGH CALCIUM PERMEABILITY AND VOLTAGE-DEPENDENT SENSITIVITY TO MAGNESIUM AND IS MEDIATED

BY GLYCINE.

SUBUNIT: HETERODIMER OF AN EPSILON SUBUNIT

AND A ZETA SUBUNIT.

SUBCELLULAR LOCATION: INTEGRAL MEMBRANE

PROTEIN.

20 SIMILARITY: BELONGS TO THE LIGAND-GATED

IONIC CHANNELS FAMILY.

SEQ ID: 44:

Description: Deletion of 114 amino acids between the positions 1257-1372 of the original protein.

Accession:

VIPS HUMAN

Name:

VASOACTIVE

INTESTINAL

POLYPEPTIDE

30

35

RECEPTOR 2

Function:

THIS IS A RECEPTOR FOR VIP AS WELL AS PACAP-38 AND -27, THE ACTIVITY OF THIS RECEPTOR IS MEDIATED BY G PROTEINS WHICH ACTIVATE ADENYLYL CYCLASE. CAN BE

COUPLED TO PHOSPHOLIPASE C.

SUBCELLULAR

LOCATION:

INTEGRAL

MEMBRANE PROTEIN.

SIMILARITY: BELONGS TO FAMILY 2 OF G-PROTEIN COUPLED RECEPTORS.

SEO ID: 45:

5

Description: Replacement of 56 C-terminal amino acids from the cytoplasmic domain of the original protein by alternative 73 amino acids.

10 SEQ ID: 46

Description: Replacement of 56 C-terminal amino acids from the cytoplasmic domain of the original protein by alternative 70 amino acids.

15

Accession:

IG1R HUMAN

Name:

INSULIN-LIKE GROWTH FACTOR I RECEPTOR

PRECURSOR

Function:

THIS RECEPTOR BINDS INSULIN-LIKE GROWTH FACTOR I (IGF I) WITH A HIGH AFFINITY AND IGF II

20

WITH A LOWER AFFINITY. IT HAS A

TYROSINE-PROTEIN KINASE ACTIVITY.

CATALYTIC ACTIVITY: ATP + A PROTEIN TYROSINE

= ADP + PROTEIN TYROSINE PHOSPHATE.

- 25

SUBUNIT: TETRAMER OF 2 ALPHA AND 2 BETA CHAINS LINKED BY DISULFIDE BONDS. THE ALPHA

CHAINS

CONTRIBUTE TO THE FORMATION OF THE LIGAND-BINDING DOMAIN, WHILE THE BETA CHAIN

CARRIES THE KINASE DOMAIN.

30

SUBCELLULAR LOCATION: TYPE I MEMBRANE

PROTEIN.

SIMILARITY: BELONGS TO THE INSULIN RECEPTOR

FAMILY OF TYROSINE- PROTEIN KINASES.

SIMILARITY: CONTAINS 2 FIBRONECTIN TYPE

III-LIKE DOMAINS.

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Description: Deletion of 22 amino acids between the positions 1268-1291 of the original protein. The deleted fragment is part of the cytoplasmic domain of INSULIN-LIKE GROWTH FACTOR I RECEPTOR, BETA-CHAIN.

Accession:

NRP HUMAN

Name:

NEUROPILIN

10 Function:

CALCIUM-INDEPENDENT CELL ADHESION MOLECULE THAT FUNCTION DURING THE FORMATION OF CERTAIN NEURONAL CIRCUITS. BINDS TO SEMAPHORIN III AND TO THE VEGF165

ISOFORM OF VEGF.

15

SUBCELLULAR LOCATION: TYPE I MEMBRANE

PROTEIN.

SIMILARITY: CONTAINS 2 CUB DOMAINS.

SIMILARITY: CONTAINS 2 F5/8 TYPE C DOMAINS.

SIMILARITY: CONTAINS 1 MAM DOMAIN.

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SEQ ID: 48

Description: Replacement of 282 C-terminal amino acids of the original protein, including the transmembrane domain and the MAM domain, by alternative 3 amino acids.

SEQ ID: 49

Description: Deletion of 83 amino acids between the positions 538-622 of the original protein. The deleted region includes part of the F5/8 TYPE C 2 domain and part of the MAM domain.

SEQ ID: 50

Description: Deletion of 385 C-terminal amino acids of the original protein, including the transmembrane domain and the MAM domain.

Accession:

FGR3 HUMAN

Name:

FIBROBLAST GROWTH FACTOR RECEPTOR 3

Function:

SUBCELLULAR LOCATION: TYPE I MEMBRANE

PROTEIN.

DISEASE: DEFECTS IN FGFR3 ARE THE CAUSE OF THE AUTOMOSOMAL DOMINANT DISEASE ACHONDROPLASIA (ACH); THE MOST FREQUENT FORM OF SHORT-LIMB DWARFISM. ACH IS CHARACTERIZED BY A LONG, NARROW TRUNK, SHORT EXTREMITIES, PARTICULARLY IN THE PROXIMAL (RHIZOMELIC) SEGMENTS, A LARGE HEAD WITH FRONTAL BOSSING, HYPOPLASIA OF THE MIDFACE AND A TRIDENT CONFIGURATION

OF THE HANDS.

DISEASE: DEFECTS IN FGFR3 ARE A CAUSE OF **ALSO CALLED** SYNDROME, CROUZON CRANIOFACIAL DYSOSTOSIS **TYPE** I (CFD1). BY CRANIOSYNOSTOSIS CHARACTERIZED (PREMATURE FUSION OF THE SKULL SUTURES), **AND EXOPHTHALMOS** HYPERTELORISM. EXTERNAL STRABISMUS, PARROT-BEAKED NOSE, SHORT UPPER LIP, HYPOPLASTIC MAXILLA, AND

A RELATIVE MANDIBULAR PROGNATHISM.

DISEASE: DEFECTS IN FGFR3 ARE A CAUSE OF THANATOPHORIC DYSPLASIA (TD) (ALSO KNOWN AS THANATOPHORIC DWARFISM), THE MOST LETHAL **SKELETAL** NEONATAL COMMON DYSPLASIA, AFFECTED INDIVIDUALS DISPLAY **FEATURES** SIMILAR TO THOSE SEEN HOMOZYGOUS ACHONDROPLASIA. IT CAUSES SEVERE SHORTENING OF THE LIMBS WITH MACROCEPHALY, NARROW THORAX AND SHORT RIBS. IN THE MOST COMMON SUBTYPE (TD1), FEMUR ARE CURVED, WHILE IN TD2, STRAIGHT FEMURS ARE ASSOCIATED WITH CLOVERLEAF SKULL.

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DISEASE: DEFECTS IN FGFR3 ARE A CAUSE OF CRANIOSYNOSTOSIS ADELAIDE TYPE (CRS3), A **FORM** OF **CORONAL SYNOSTOSIS** (CS) **CHARACTERIZED** BY CRANIOSYNOSTOSIS, **MIDFACE** HYPOPLASIA, DOWNSLANDING PALPEBRAL FISSURES, PTOSIS, HIGHLY ARCHED MID-TO-MODERATE PALATE. **SENSORINEURAL** HEARING LOSS, NORMAL STATURE, BRADYDACTYLY, BROAD BIG TOES. RADIOLOGICALY HANDS AND FEET **SHOW** MIDDLE PHALANGES. THIMBLE-LIKE CONED EPIPHYSES, AND CARPAL AND TARSAL FUSIONS. DISEASE: DEFECTS IN FGFR3 ARE A CAUSE OF THE AUTOSOMAL **DOMINANT DISEASE** HYPO-CHARACTERIZED CHONDROPLASIA BY STATURE. DISPROPORTIONATE SHORT IT RESEMBLE ACHONDROPLASIA, BUT WITH A LESS SEVERE PHENOTYPE. SIMILARITY: BELONGS TO THE FIBROBLAST GROWTH FACTOR RECEPTOR FAMILY. SIMILARITY: CONTAINS 3 IMMUNOGLOBULIN-LIKE DOMAINS.

SEQ ID: 51

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Description: Replacement of 496 C-terminal amino acids of the original protein by alternative 79 amino acids. The deleted region includes the C-terminal part of the extracellular domain, the transmembrane domain, the cytoplasmic domain, the protein kinase domain and the two ATP binding domains.

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EGF MOUSE

EPIDERMAL GROWTH FACTOR

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FUNCTION: THE GROWTH FACTOR STIMULATES THE GROWTH OF VARIOUS EPIDERMAL AND EPITHELIAL TISSUES IN VIVO AND IN VITRO AND OF SOME FIBROBLASTS IN CELL CULTURE.
SUBCELLULAR LOCATION: TYPE I MEMBRANE PROTEIN.

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SIMILARITY: CONTAINS 8 COMPLETE AND ONE INCOMPLETE EGF-LIKE DOMAINS.

SEQ ID NO: 52

Deletion of 144 amino acids between the positions 1020-1165, including the transmembrane domain and part of the cytoplasmic domain of the original protein.

10 **SEQ ID NO : 53**

Replacement of 418 C-terminal amino acids of the original protein by alternative 5 amino acids. The deleted region includes the EGF active chain, 4 out of 9 EGF-like domains within the extracellular region of the protein, the transmembrane and the cytoplasmic regions.

SEQ ID NO: 54

Deletion of 641 amino acids between the positions 66-707 of the original protein.

The deleted region is in the extracellular part of the protein and it includes 4 out of 9 EGF-like domains. NV-20 contains the original signal peptide, part of the extracellular domain, the epidermal growth factor chain (located between the positions 977-1029 of the original protein), and the original transmembrane and the cytoplasmic domains.

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SEQ ID NO: 55

Deletion of 842 amino acids between the positions 17-859 of the original protein (including replacement of the amino acid in the position 859 by an alternative one). The deleted region is in the extracellular part of the protein and it includes 5 out of 9 EGF-like domains. NV-20 contains the original signal peptide, part of the extracellular domain, the epidermal growth factor chain (located between the positions 977-1029 of the original protein), and the original transmembrane and the cytoplasmic domains.

ACE_MOUSE

FUNCTION: CONVERTS ANGIOTENSIN I TO ANGIOTENSIN II BY RELEASE OF THE TERMINAL HIS-LEU,THIS RESULTS IN AN INCREASE OF THE VASOCONSTRICTOR ACTIVITY OF ANGIOTENSIN. CATALYTIC ACTIVITY: RELEASE OF A C-TERMINAL DIPEPTIDE, OLIGOPEPTIDE-|-XAA-XBB, WHEN XAA IS NOT PRO, AND XBB IS NEITHER ASP NOR GLU. CONVERTS ANGIOTENSIN I TO ANGIOTENSIN II.

10 COFACTOR: BINDS TWO ZINC IONS (BY SIMILARITY).
SUBCELLULAR LOCATION: TYPE I MEMBRANE PROTEIN.
ALTERNATIVE PRODUCTS: THE TESTICULAR ANGIOTENSINCONVERTING ENZYME IS TRANSCRIBED FROM THE SAME GENE AS
THE SOMATIC ISOFORM, PROBABLY FROM AN ALTERNATIVE START
15 SITE.

SIMILARITY: BELONGS TO PEPTIDASE FAMILY M2 (ZINC METALLOPROTEASE).

20 SEQ ID NO: 56

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Replacement of 77 C-terminal amino acids of the original protein, including the entire transmembrane and cytoplasmic domains, by alternative 14 amino acids.

ESR1_MOUSE

ESTROGEN RECEPTOR

- FUNCTION: THE STEROID HORMONES AND THEIR RECEPTORS ARE INVOLVED IN THE REGULATION OF EUKARYOTIC GENE EXPRESSION AND AFFECT CELLULAR PROLIFERATION AND DIFFERENTIATION IN TARGET TISSUES.

 SUBUNIT: HOMODIMER.
- 35 SUBCELLULAR LOCATION: NUCLEAR.
 DOMAIN: COMPOSED OF THREE DOMAINS: A MODULATING
 N-TERMINAL DOMAIN, A DNA-BINDING DOMAIN AND A
 C-TERMINAL STEROID-BINDING DOMAIN.
 MISCELLANEOUS: IN THE ABSENCE OF LIGAND, STEROID HORMONE
- RECEPTORS ARE THOUGHT TO BE WEAKLY ASSOCIATED WITH NUCLEAR COMPONENTS; HORMONE BINDING GREATLY INCREASES RECEPTOR AFFINITY. THE HORMONE-RECEPTOR COMPLEX APPEARS TO RECOGNIZE DISCRETE DNA SEQUENCES UPSTREAM OF TRANSCRIPTIONAL START SITES.

SIMILARITY: BELONGS TO THE NUCLEAR HORMONE RECEPTORS FAMILY. NR3 SUBFAMILY.

SEQ ID: 57

Replacement of 229 C-terminal amino acids of the original protein, including part of the steroid-binding domain, by an alternative 12 amino acids.

FA7_MOUSE

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COAGULATION FACTOR VII PRECURSOR

FUNCTION: CIRCULATES IN THE BLOOD IN A ZYMOGEN FORM. FACTOR VII IS CONVERTED TO FACTOR VIIA BY FACTOR XA, FACTOR XIIA, FACTOR IXA, OR THROMBIN BY MINOR PROTEOLYSIS. IN THE PRESENCE OF TISSUE FACTOR AND CALCIUM IONS, FACTOR VIIA THEN CONVERTS FACTOR X TO FACTOR XA BY LIMITED PROTEOLYSIS. FACTOR VIIA WILL ALSO CONVERT FACTOR IX TO FACTOR IXA IN THE PRESENCE OF TISSUE FACTOR AND CALCIUM (BY SIMILARITY).

CATALYTIC ACTIVITY: HYDROLYSES ONE ARG-|-ILE BOND IN

FACTOR X TO FORM FACTOR XA.

SUBUNIT: HETERODIMER OF A LIGHT CHAIN AND A HEAVY CHAIN LINKED BY A DISULFIDE BOND (BY SIMILARITY).

TISSUE SPECIFICITY: PLASMA.

PTM: THE VITAMIN K-DEPENDENT, ENZYMATIC CARBOXYLATION OF SOME GLUTAMIC ACID RESIDUES ALLOWS THE MODIFIED PROTEIN TO BIND CALCIUM (BY SIMILARITY).

SIMILARITY: CONTAINS 2 EGF-LIKE DOMAINS.

SIMILARITY: BELONGS TO PEPTIDASE FAMILY S1; ALSO KNOWN AS

THE TRYPSIN FAMILY.

35 SEQ ID: 58

Deletion of 101 amino acids, between the positions 119-220 of the original protein. The deleted region contains 74 amino acids from the C-terminal end of the factor VII light chain, and 26 amino acids from the N-terminal end of the factor VII heavy catalytic chain. The deleted region includes EGF-like 2 domain and the cleavage site (by factor XA, factor XIIA, factor IXA, or thrombin) of

the original protein.

CALO_MOUSE

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CALCITONIN PRECURSOR

FUNCTION: CAUSES A RAPID BUT SHORT-LIVED DROP IN THE LEVEL OF CALCIUM AND PHOSPHATE IN BLOOD BY PROMOTING THE INCORPORATION OF THOSE IONS IN THE BONES.

ALTERNATIVE PRODUCTS: THE CALCITONIN PRECURSOR AND THE CALCITONIN RELATED PEPTIDE PRECURSOR ARE OBTAINED BY TISSUE-SPECIFIC SPLICING OF THE SAME GENE.

SIMILARITY: BELONGS TO THE CALCITONIN FAMILY.

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SEO ID NO: 59

Deletion of 33 amino acids, spanning the positions 18-50, between the signal and the calcitonin peptide in the original precursor protein.

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gi 2826776

VESICULAR INHIBITORY AMINO ACID TRANSPORTER

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function="uptake of GABA and glycine into synaptic vesicles"

SEQ ID NO: 60

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Replacement of the last 7 C-terminal amino acids of the original protein by alternative 11 amino acids.

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PTI6_HUMAN

PLACENTAL THROMBIN INHIBITOR

CYTOPLASMIC ANTIPROTEINASE, PROTEASE INHIBITOR 6.
SIMILARITY: BELONGS TO THE SERPIN FAMILY. OV-SERPIN SUBFAMILY.

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SEQ ID NO: 61

Replacement of the last 4 C-terminal amino acids of the original protein by alternative 28 amino acids.

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SEQ ID NO: 62

Replacement of the last 16 C-terminal amino acids of the original protein by alternative 12 amino acids.

RIN1 HUMAN

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RAS INTERACTION/INTERFERENCE PROTEIN 1 (RAS INHIBITOR JC99) (FRAGMENT)

SEQ ID NO: 63

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Replacement of 158 last C-terminal amino acids of the original protein by alternative 71 amino acids with probable transmembrane region.

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CDNC_HUMAN

CYCLIN-DEPENDENT KINASE INHIBITOR 1C P57

FUNCTION: POTENT TIGHT-BINDING INHIBITOR OF SEVERAL G1 CYCLIN/CDK COMPLEXES (CYCLIN E-CDK2, CYCLIN D2-CDK4, AND CYCLIN A-CDK2) AND, TO LESSER EXTENT, OF THE MITOTIC CYCLIN B-CDC2. NEGATIVE REGULATOR OF CELL PROLIFERATION. MAY PLAY A ROLE IN MAINTENANCE OF THE NONPROLIFERATIVE STATE THROUGHOUT LIFE.

SUBCELLULAR LOCATION: NUCLEAR (BY SIMILARITY). DISEASE: CDKN1C MUTATIONS ARE INVOLVED IN TUMOR FORMATION.

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SEQ ID NO: 64

Addition of 121 amino acids at the N-terminus of the protein.

CDN2_HUMAN

CYCLIN-DEPENDENT KINASE 4 INHIBITOR A (CDK4I) (MULTIPLE TUMOR SUPPRESSOR 1) (MTS1)

FUNCTION: INTERACTS STRONGLY WITH CDK4 AND CDK6. INHIBITS ITS ABILITY TO INTERACT WITH CYCLINS D. COULD ACT AS A NEGATIVE REGULATOR OF THE PROLIFERATION OF NORMAL CELLS.

SUBUNIT: HETERODIMER WITH CDK4 OR CDK6.

DISEASE: CDKN2A MUTATIONS ARE INVOLVED IN TUMOR

15 FORMATION IN A WIDE RANGE OF TISSUES.

SIMILARITY: BELONGS TO THE CDKN2 FAMILY OF CYCLIN-DEPENDENT KINASE INHIBITORS.

SIMILARITY: CONTAINS 4 ANK REPEATS.

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SEQ ID NO: 65

Replacement of 5 amino acids at the positions 18, 24, 27, 30, 37 of the original protein by alternative amino acids. Replacement of last 4 C-terminal amino acids of the original protein by alternative 20 amino acids.

CDN5_HUMAN

30

CYCLIN-DEPENDENT KINASE 4 INHIBITOR B (MULTIPLE TUMOR SUPPRESSOR 2)

FUNCTION: INTERACTS STRONGLY WITH CDK4 AND CDK6. POTENT INHIBITOR. POTENTIAL EFFECTOR OF TGF-BETA INDUCED CELL CYCLE ARREST.

SUBUNIT: HETERODIMER OF P14 WITH CDK4.

DISEASE: CDKN2B MUTATIONS ARE INVOLVED IN TUMOR FORMATION.

SIMILARITY: BELONGS TO THE CDKN2 FAMILY OF

40 CYCLIN-DEPENDENT KINASE INHIBITORS. SIMILARITY: CONTAINS 2 ANK REPEATS.

SEQ ID NO: 66

Replacement of the last 6 C-terminal amino acids of the original protein by alternative 52 amino acids.

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HEP2 HUMAN

HEPARIN COFACTOR II PRECURSOR PROTEASE INHIBITOR LEUSERPIN 2

10

FUNCTION: THROMBIN INHIBITOR ACTIVATED BY THE GLYCOSAMINOGLYCANS, HEPARIN OR DERMATAN SULFATE. IN THE PRESENCE OF THE LATTER, HC-II BECOMES THE PREDOMINANT THROMBIN INHIBITOR IN PLACE OF ANTITHROMBIN III (AT). ALSO INHIBITS CHYMOTRYPSIN, BUT IN A GLYCOSAMINOGLYCAN-

INDEPENDENT MANNER.
FUNCTION: PEPTIDES AT THE N-TERMINAL OF HC-II HAVE CHEMOTACTIC ACTIVITY FOR BOTH MONOCYTES AND NEUTROPHILS.

TISSUE SPECIFICITY: EXPRESSED PREDOMINANTLY IN LIVER.

DOMAIN: THE N-TERMINAL ACIDIC REPEAT REGION MEDIATES, IN PART, THE

GLYCOSAMINOGLYCAN-ACCELERATED THROMBIN INHIBITION.
DISEASE: DEFECTS IN HCF2 ARE ASSOCIATED WITH THROMBOSIS
(THROMBOPHILIA).

25 (THROMBOPHILIA).

SIMILARITY: BELONGS TO THE SERPIN FAMILY.

SEQ ID NO: 67

Deletion of 150 amino acids, between the positions 334-485, of the original protein. The deleted region includes the reactive bond (the active site) of the original protein. NV-33 does contain the chemotactic activity domain, the glycosaminoglycan-binding site and the hirudin-like 2 x 11 AA approximate repeats, Asp/Glu rich.

35

TFP2_HUMAN

TISSUE FACTOR PATHWAY INHIBITOR 2 PRECURSOR

40

FUNCTION: SEEMS TO INHIBIT TRYPSIN, FACTOR VII(A)/TISSUE FACTOR, WEAKLY FACTOR XA. HAS NO EFFECT ON THROMBIN.

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DOMAIN: THIS INHIBITOR CONTAINS THREE INHIBITORY DOMAINS. SIMILARITY: BELONGS TO THE BPTI/KUNITZ FAMILY OF INHIBITORS. HIGHLY SIMILAR TO TPFI.

5 **SEQ ID NO: 68**

Replacement of 36 C-terminal amino acids of the original protein by alternative 12 amino acids. The deleted region includes part of the BPTI/KUNITZ inhibitor domain-3 and the poly-Lysine domain of the original protein.

10

SEQ ID NO: 69

Deletion of 25 amino acids, between the positions 153-178 of the original protein, and replacement of the amino acid at the position 179 by alternative one. The deleted region includes the active site and part of the BPTI/KUNITZ inhibitor domain-3.

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TFPI_HUMAN

TISSUE FACTOR PATHWAY INHIBITOR PRECURSOR (TFPI)

25 **SEQ ID NO: 70**

Replacement of 95 C-terminal amino acids of the original protein, containing the entire BPTI/KUNITZ inhibitor-3 domain, by aternative 16 amino acids.

30

Example II: Variant nucleic acid sequence

The nucleic acid sequences of the invention include nucleic acid sequences which encode variant product and fragments and analogs thereof. The nucleic acid sequences may alternatively be sequences complementary to the above coding sequence, or to a region of said coding sequence. The length of the complementary sequence is sufficient to avoid the expression of the coding sequence. The nucleic acid sequences may be in the form of RNA or in the form of DNA, and include messenger RNA, synthetic RNA and DNA, cDNA, and genomic DNA. The DNA may be double-stranded or single-stranded, and if

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single-stranded may be the coding strand or the non-coding (anti-sense, complementary) strand. The nucleic acid sequences may also both include dNTPs, rNTPs as well as non naturally occurring sequences. The sequence may also be a part of a hybrid between an amino acid sequence and a nucleic acid 5 sequence.

In a general embodiment, the nucleic acid sequence has at least 90%, identity with any one of the sequence identified as SEQ ID NO: 1 to SEQ ID NO: 174 provided that this sequence is not completely identical with that of the original sequence.

10

The nucleic acid sequences may include the coding sequence by itself. By another alternative the coding region may be in combination with additional coding sequences, such as those coding for fusion protein or signal peptides, in combination with non-coding sequences, such as introns and control elements. promoter and terminator elements or 5' and/or 3' untranslated regions, effective for expression of the coding sequence in a suitable host, and/or in a vector or host environment in which the variant nucleic acid sequence is introduced as a heterologous sequence.

The nucleic acid sequences of the present invention may also have the product coding sequence fused in-frame to a marker sequence which allows for 20 purification of the variant product. The marker sequence may be, for example, a hexahistidine tag to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al. Cell 37:767 (1984)).

Also included in the scope of the invention are fragments as defined above also referred to herein as oligonucleotides, typically having at least 20 bases, preferably 20-30 bases corresponding to a region of the coding-sequence nucleic acid sequence. The fragments may be used as probes, primers, and when WO 01/36632 PCT/IL00/00766

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complementary also as antisense agents, and the like, according to known methods.

As indicated above, the nucleic acid sequence may be substantially a depicted in any one of SEQ ID NO: 1 to SEQ ID NO: 87 or fragments thereof or sequences having at least 90% identity to the above sequence as explained above. Alternatively, due to the degenerative nature of the genetic code, the sequence may be a sequence coding for any one of the amino acid sequence of SEQ ID NO: 88 to SEQ ID NO: 174, or fragments or analogs of said amino acid sequence.

10

A. Preparation of nucleic acid sequences

The nucleic acid sequences may be obtained by screening cDNA libraries using oligonucleotide probes which can hybridize to or PCR-amplify nucleic acid sequences which encode the variant products disclosed above. cDNA libraries prepared from a variety of tissues are commercially available and procedures for screening and isolating cDNA clones are well-known to those of skill in the art. Such techniques are described in, for example, Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual (2nd Edition), Cold Spring Harbor Press, Plainview, N.Y. and Ausubel FM et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y.

The nucleic acid sequences may be extended to obtain upstream and downstream sequences such as promoters, regulatory elements, and 5' and 3' untranslated regions (UTRs). Extension of the available transcript sequence may be performed by numerous methods known to those of skill in the art, such as PCR or primer extension (Sambrook et al., supra), or by the RACE method using, for example, the Marathon RACE kit (Clontech, Cat. # K1802-1).

Alternatively, the technique of "restriction-site" PCR (Gobinda et al. PCR Methods Applic. 2:318-22, (1993)), which uses universal primers to retrieve flanking sequence adjacent a known locus, may be employed. First, genomic DNA is amplified in the presence of primer to a linker sequence and a primer

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specific to the known region. The amplified sequences are subjected to a second round of PCR with the same linker primer and another specific primer internal to the first one. Products of each round of PCR are transcribed with an appropriate RNA polymerase and sequenced using reverse transcriptase.

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Inverse PCR can be used to amplify or extend sequences using divergent primers based on a known region (Triglia, T. et al., Nucleic Acids Res. 16:8186, (1988)). The primers may be designed using OLIGO(R) 4.06 Primer Analysis Software (1992; National Biosciences Inc, Plymouth, Minn.), or another appropriate program, to be 22-30 nucleotides in length, to have a GC content of 10 50% or more, and to anneal to the target sequence at temperatures about 68-72°C. The method uses several restriction enzymes to generate a suitable fragment in the known region of a gene. The fragment is then circularized by intramolecular ligation and used as a PCR template.

Capture PCR (Lagerstrom, M. et al., PCR Methods Applic. 1:111-19, 15 (1991)) is a method for PCR amplification of DNA fragments adjacent to a known sequence in human and yeast artificial chromosome DNA. Capture PCR also requires multiple restriction enzyme digestions and ligations to place an engineered double-stranded sequence into a flanking part of the DNA molecule before PCR.

Another method which may be used to retrieve flanking sequences is that of Parker, J.D., et al., Nucleic Acids Res., 19:3055-60, (1991)). Additionally, one can use PCR, nested primers and PromoterFinder™ libraries to "walk in" genomic DNA (PromoterFinder™; Clontech, Palo Alto, CA). This process avoids the need to screen libraries and is useful in finding intron/exon junctions. Preferred 25 libraries for screening for full length cDNAs are ones that have been size-selected to include larger cDNAs. Also, random primed libraries are preferred in that they will contain more sequences which contain the 5' and upstream regions of genes.

A randomly primed library may be particularly useful if an oligo d(T) library does not yield a full-length cDNA. Genomic libraries are useful for 30 extension into the 5' nontranslated regulatory region.

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The nucleic acid sequences and oligonucleotides of the invention can also be prepared by solid-phase methods, according to known synthetic methods. Typically, fragments of up to about 100 bases are individually synthesized, then joined to form continuous sequences up to several hundred bases.

5

B. Use of variant nucleic acid sequence for the production of variant products

In accordance with the present invention, nucleic acid sequences specified above may be used as recombinant DNA molecules that direct the expression of variant products.

As will be understood by those of skill in the art, it may be advantageous to produce variant product-encoding nucleotide sequences possessing codons other than those which appear in any one of SEQ ID NO: 1 to SEQ ID NO: 87 which are those which naturally occur in the human genome. Codons preferred by a particular prokaryotic or eukaryotic host (Murray, E. et al. Nuc Acids Res., 17:477-508, (1989)) can be selected, for example, to increase the rate of variant product expression or to produce recombinant RNA transcripts having desirable properties, such as a longer half-life, than transcripts produced from naturally occurring sequence.

The nucleic acid sequences of the present invention can be engineered in order to alter a variant product coding sequence for a variety of reasons, including but not limited to, alterations which modify the cloning, processing and/or expression of the product. For example, alterations may be introduced using techniques which are well known in the art, e.g., site-directed mutagenesis, to insert new restriction sites, to alter glycosylation patterns, to change codon preference, etc.

The present invention also includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs comprise a vector, such as a plasmid or viral vector, into which a nucleic acid sequence of the invention has been inserted, in a forward or reverse orientation.

In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are also described in Sambrook, et al., (supra).

The present invention also relates to host cells which are genetically engineered with vectors of the invention, and the production of the product of the invention by recombinant techniques. Host cells are genetically engineered (i.e., transduced, transformed or transfected) with the vectors of this invention which may be, for example, a cloning vector or an expression vector. The vector may be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the expression of the variant nucleic acid sequence. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to those skilled in the art.

The nucleic acid sequences of the present invention may be included in any one of a variety of expression vectors for expressing a product. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; baculovirus; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other vector may be used as long as it is replicable and viable in the host.

The appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease site(s) by procedures known in the art. Such procedures and related sub-cloning procedures are deemed to be within the scope of those skilled in the art.

The DNA sequence in the expression vector is operatively linked to an appropriate transcription control sequence (promoter) to direct mRNA synthesis. Examples of such promoters include: LTR or SV40 promoter, the *E.coli lac* or trp promoter, the phage lambda PL promoter, and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation, and a transcription terminator. The vector may also include appropriate sequences for amplifying expression. In addition, the expression vectors preferably contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or amplicillin resistance in *E.coli*.

The vector containing the appropriate DNA sequence as described above, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. Examples of appropriate expression hosts include: bacterial cells, such as *E.coli*, *Streptomyces, Salmonella typhimurium*; fungal cells, such as yeast; insect cells such as *Drosophila* and *Spodoptera* Sf9; animal cells such as CHO, COS, HEK 293 or Bowes melanoma; adenoviruses; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein. The invention is not limited by the host cells employed.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the variant product. For example, when large quantities of variant product are needed for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be desirable. Such vectors include, but are not limited to, multifunctional *E.coli* cloning and expression vectors such as *Bluescript*(R) (Stratagene), in which the variant polypeptide coding sequence may be ligated into the vector in-frame with sequences for the amino-terminal Met and the subsequent 7 residues of beta-galactosidase so that a hybrid protein is produced;

pIN vectors (Van Heeke & Schuster J. Biol. Chem. 264:5503-5509, (1989)); pET vectors (Novagen, Madison WI); and the like.

In the yeast Saccharomyces cerevisiae a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase and 5 PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al., (Methods in Enzymology 153:516-544, (1987)).

In cases where plant expression vectors are used, the expression of a sequence encoding variant product may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV (Brisson et al., Nature 310:511-514. (1984)) may be used alone or in combination with the omega leader sequence from TMV (Takamatsu et al., EMBO J., 6:307-311, (1987)). Alternatively, plant promoters such as the small subunit of RUBISCO (Coruzzi et al., EMBO J. 3:1671-1680, (1984); Broglie et al., Science 224:838-843, (1984)); or heat shock promoters (Winter J and Sinibaldi R.M., Results Probl. Cell Differ., 17:85-105, (1991)) may be used. These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. For reviews of such techniques, see Hobbs S. or Murry L.E. (1992) in McGraw Hill Yearbook of Science and Technology, McGraw Hill, New York, N.Y., pp 191-196; or Weissbach and Weissbach (1988) Methods for Plant Molecular Biology, Academic Press, New York, N.Y., pp 421-463.

Variant product may also be expressed in an insect system. In one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The variant product coding sequence may be cloned into a nonessential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of variant coding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein coat. The recombinant viruses are then used to infect *S. frugiperda* cells or

Trichoplusia larvae in which variant protein is expressed (Smith et al., J. Virol. 46:584, (1983); Engelhard, E.K. et al., Proc. Nat. Acad. Sci. 91:3224-7, (1994)).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, a variant product coding sequence may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a nonessential E1 or E3 region of the viral genome will result in a viable virus capable of expressing variant protein in infected host cells (Logan and Shenk, *Proc. Natl. Acad. Sci.* 81:3655-59, (1984). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be required for efficient translation of a variant product coding sequence. These signals include the ATG initiation codon and adjacent sequences. In cases where variant product coding sequence, its initiation codon and upstream sequences are inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous transcriptional control signals including the ATG initiation codon must be provided. Furthermore, the initiation codon must be in the correct reading frame to ensure transcription of the entire insert. Exogenous transcriptional elements and initiation codons can be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (Scharf, D. et al., (1994) Results Probl. Cell Differ., 20:125-62, (1994); Bittner et al., Methods in Enzymol 153:516-544, (1987)).

In a further embodiment, the present invention relates to host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell.

Introduction of the construct into the host cell can be effected by calcium

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phosphate transfection, DEAE-Dextran mediated transfection, or electroporation (Davis, L., Dibner, M., and Battey, I. (1986) Basic Methods in Molecular Biology). Cell-free translation systems can also be employed to produce polypeptides using RNAs derived from the DNA constructs of the present invention.

A host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the protein include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Post-translational processing which cleaves a "pre-pro" form of the protein may also be important for correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, 293, WI38, etc. have specific cellular machinery and characteristic mechanisms for such post-translational activities and may be chosen to ensure the correct modification and processing of the introduced, foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express variant product may be transformed using expression vectors which contain viral origins of replication or endogenous expression elements and a selectable marker gene.

Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clumps of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler M., et al., Cell 11:223-32, (1977)) and adenine phosphoribosyltransferase (Lowy I., et al., Cell 22:817-23, (1980)) genes which can be employed in tk- or aprt- cells, respectively. Also, antimetabolite,

antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler M., et al., Proc. Natl. Acad. Sci. 77:3567-70, (1980)); npt, which confers resistance to the aminoglycosides neomycin and G-418 (Colbere-Garapin, F. et al., J. Mol. Biol., 5 150:1-14, (1981)) and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, supra). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman S.C. and R.C. Mulligan, Proc. Natl. Acad. Sci. 10 85:8047-51, (1988)). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate, GUS, and luciferase and its substrates, luciferin and ATP, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C.A. et. al., 15 Methods Mol. Biol., 55:121-131, (1995)).

Host cells transformed with a nucleotide sequence encoding variant product may be cultured under conditions suitable for the expression and recovery of the encoded protein from cell culture. The product produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing nucleic acid sequences encoding variant product can be designed with signal sequences which direct secretion of variant product through a prokaryotic or eukaryotic cell membrane.

The variant product may also be expressed as a recombinant protein with one or more additional polypeptide domains added to facilitate protein purification. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp, Seattle, Wash.). The

inclusion of a protease-cleavable polypeptide linker sequence between the purification domain and variant product is useful to facilitate purification. One such expression vector provides for expression of a fusion protein compromising a variant polypeptide fused to a polyhistidine region separated by an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography, as described in Porath, et al., Protein Expression and Purification, 3:263-281, (1992)) while the enterokinase cleavage site provides a means for isolating variant polypeptide from the fusion protein pGEX vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to ligand-agarose beads (e.g., glutathione-agarose in the case of GST-fusions) followed by elution in the presence of free ligand.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents, or other methods, which are well know to those skilled in the art.

The variant products can be recovered and purified from recombinant cell cultures by any of a number of methods well known in the art, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high

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performance liquid chromatography (HPLC) can be employed for final purification steps.

C. Diagnostic applications utilizing nucleic acid sequences

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The nucleic acid sequences of the present invention may be used for a variety of diagnostic purposes. The nucleic acid sequences may be used to detect and quantitate expression of the variant in patient's cells, e.g. biopsied tissues, by detecting the presence of mRNA coding for variant product. Alternatively, the assay may be used to detect soluble variant in the serum or blood. This assay typically involves obtaining total mRNA from the tissue or serum and contacting the mRNA with a nucleic acid probe. The probe is a nucleic acid molecule of at least 20 nucleotides, preferably 20-30 nucleotides, capable of specifically hybridizing with a sequence included within the sequence of a nucleic acid molecule encoding variant product under hybridizing conditions, detecting the presence of mRNA hybridized to the probe, and thereby detecting the expression of variant. This assay can be used to distinguish between absence, presence, and excess expression of variant product and to monitor levels of variant expression during therapeutic intervention. In addition, the assay may be used to compare the levels of the variant of the invention to the levels of the original sequence from which it has been varied or to levels of other variants, which comparison may have some physiological meaning.

The invention also contemplates the use of the nucleic acid sequences as a diagnostic for diseases resulting from inherited defective variant sequences, or diseases in which the ratio of the amount of the original sequence from which the variant was varied to the novel variants of the invention is altered. These sequences can be detected by comparing the sequences of the defective (i.e., mutant) variant coding region with that of a normal coding region. Association of the sequence coding for mutant variant product with abnormal variant product activity may be verified. In addition, sequences encoding mutant variant products can be inserted into a suitable vector for expression in a functional assay system WO 01/36632 PCT/IL00/00766

(e.g., colorimetric assay, complementation experiments in a variant protein deficient strain of HEK293 cells) as yet another means to verify or identify mutations. Once mutant genes have been identified, one can then screen populations of interest for carriers of the mutant gene.

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Individuals carrying mutations in the nucleic acid sequence of the present invention may be detected at the DNA level by a variety of techniques. Nucleic acids used for diagnosis may be obtained from a patient's cells, including but not limited to such as from blood, urine, saliva, placenta, tissue biopsy and autopsy material. Genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki, et al., Nature 324:163-166, (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid of the present invention can be used to identify and analyze mutations in the gene of the present invention. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype.

Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA of the invention or alternatively, radiolabeled antisense DNA sequences of the invention. Sequence changes at specific locations may also be revealed by nuclease protection assays, such RNase and S1 protection or the 20 chemical cleavage method (e.g. Cotton, et alProc. Natl. Acad. Sci. USA, 85:4397-4401, (1985)), or by differences in melting temperatures. "Molecular beacons" (Kostrikis L.G. et al., Science 279:1228-1229, (1998)), hairpin-shaped, single-stranded synthetic oligo- nucleotides containing probe sequences which are complementary to the nucleic acid of the present invention, may also be used 25 to detect point mutations or other sequence changes as well as monitor expression levels of variant product. Such diagnostics would be particularly useful for prenatal testing.

Another method for detecting mutations uses two DNA probes which are designed to hybridize to adjacent regions of a target, with abutting bases, where the region of known or suspected mutation(s) is at or near the abutting bases.

The two probes may be joined at the abutting bases, e.g., in the presence of a ligase enzyme, but only if both probes are correctly base paired in the region of probe junction. The presence or absence of mutations is then detectable by the presence or absence of ligated probe.

Also suitable for detecting mutations in the variant product coding sequence are oligonucleotide array methods based on sequencing by hybridization (SBH), as described, for example, in U.S. Patent No. 5,547,839. In a typical method, the DNA target analyte is hybridized with an array of oligonucleotides formed on a microchip. The sequence of the target can then be "read" from the pattern of target binding to the array.

D. Gene mapping utilizing nucleic acid sequences

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The nucleic acid sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with disease.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 20-30 bp) from the variant cDNA. Computer analysis of the 3' untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, which would complicate the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids or using instead radiation hybrids

or are rapid procedures for assigning a particular DNA to a particular chromosome.

Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include in situ hybridization, prescreening with labeled flow-sorted chromosomes and preselection by hybridization to construct chromosome specific-cDNA libraries.

Fluorescence in situ hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 50 or 60 bases. For a review of this technique, see Verma et al., Human Chromosomes: a Manual of Basic Techniques, (1988) Pergamon Press, New York.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in the OMIM database (Center for Medical Genetics, Johns Hopkins University, Baltimore, MD and National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD). The OMIM gene map presents the cytogenetic map location of disease genes and other expressed genes. The OMIM database provides information on diseases associated with the chromosomal location. Such associations include the results of linkage analysis mapped to this interval, and the correlation of translocations and other chromosomal aberrations in this area with the advent of polygenic diseases, such as cancer, in general and prostate cancer in particular.

E. Therapeutic applications of nucleic acid sequences

Nucleic acid sequences of the invention may also be used for therapeutic purposes. Turning first to the second aspect of the invention (i.e. inhibition of expression of variant), expression of variant product may be modulated through 5 antisense technology, which controls gene expression through hybridization of complementary nucleic acid sequences, i.e. antisense DNA or RNA, to the control, 5' or regulatory regions of the gene encoding variant product. For example, the 5' coding portion of the nucleic acid sequence sequence which codes for the product of the present invention is used to design an antisense oligonucleotide of from about 10 to 40 base pairs in length. Oligonucleotides derived from the transcription start site, e.g. between positions -10 and +10 from the start site, are preferred. An antisense DNA oligonucleotide is designed to be complementary to a region of the nucleic acid sequence involved in transcription (Lee et al., Nucl. Acids, Res., 6:3073, (1979); Cooney et al., Science 241:456, 15 (1988); and Dervan et al., Science 251:1360, (1991)), thereby preventing transcription and the production of the variant products. An antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into the variant products (Okano J. Neurochem. 56:560, (1991)). The antisense constructs can be delivered to cells by procedures known in the art such that the antisense RNA or DNA may be expressed in vivo. The antisense may be antisense mRNA or DNA sequence capable of coding such antisense mRNA. The antisense mRNA or the DNA coding thereof can be complementary to the full sequence of nucleic acid sequences coding for the variant protein or to a fragment of such a sequence which is sufficient to inhibit production of a protein product.

Turning now to the first aspect of the invention, i.e. expression of variant, expression of variant product may be increased by providing coding sequences for coding for said product under the control of suitable control elements ending its expression in the desired host.

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The nucleic acid sequences of the invention may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The formulation should suit the mode of administration.

The products of the invention as well as any activators and deactivators compounds (see below) which are polypeptides, may also be employed in accordance with the present invention by expression of such polypeptides in vivo, which is often referred to as "gene therapy." Cells from a patient may be engineered with a nucleic acid sequence (DNA or RNA) encoding a polypeptide ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, cells may be engineered by procedures known in the art by use of a retroviral particle containing RNA encoding a polypeptide of the present invention.

Similarly, cells may be engineered in vivo for expression of a polypeptide in vivo by procedures known in the art. As known in the art, a producer cell for producing a retroviral particle containing RNA encoding the polypeptide of the present invention may be administered to a patient for engineering cells in vivo and expression of the polypeptide in vivo. These and other methods for administering a product of the present invention by such method should be apparent to those skilled in the art from the teachings of the present invention. For example, the expression vehicle for engineering cells may be other than a retrovirus, for example, an adenovirus which may be used to engineer cells in vivo after combination with a suitable delivery vehicle.

Retroviruses from which the retroviral plasmid vectors mentioned above may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, adenovirus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, psi-2, psi-AM, PA12, T19-14X, VT-19-17-H2, psi-CRE, psi-CRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller (Human Gene Therapy, Vol. 1, pg. 5-14, (1990)). The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO₄ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include the nucleic acid sequence(s) encoding the polypeptides. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express the nucleic acid sequence(s) encoding the polypeptide. Eukaryotic cells which may be transduced include, but are not limited to, embryonic stem cells, embryonic carcinoma cells, as well as hematopoietic stem cells, hepatocytes, fibroblasts, myoblasts, keratinocytes, endothelial cells, and bronchial epithelial cells.

The genes introduced into cells may be placed under the control of inducible promoters, such as the radiation-inducible Egr-1 promoter, (Maceri, H.J., et al., Cancer Res., 56(19):4311 (1996)), to stimulate variant production or antisense inhibition in response to radiation, eg., radiation therapy for treating tumors.

25 Example III. Variant product

The substantially purified variant product of the invention has been defined above as the product coded from the nucleic acid sequence of the invention. Preferably the amino acid sequence is an amino acid sequence having at least 90% identity to any one of the sequences identified as SEQ ID NO: 88 to SEQ ID NO: 174 provided that the amino acid sequence is not identical to that of

the original sequence from which it has been varied. The protein or polypeptide may be in mature and/or modified form, also as defined above. Also contemplated are protein fragments having at least 10 contiguous amino acid residues, preferably at least 10-20 residues, derived from the variant product, as well as homologues as explained above.

The sequence variations are preferably those that are considered conserved substitutions, as defined above. Thus, for example, a protein with a sequence having at least 90% sequence identity with any of the products identified as SEQ ID NO: 88 to SEQ ID NO: 174, preferably by utilizing conserved substitutions as defined above is also part of the invention, and provided that it is not identical to the original peptide from which it has been varied. In a more specific embodiment, the protein has or contains any one of the sequence identified as SEQ ID NO: 88 to SEQ ID NO: 174. The variant product may be (i) one in which one or more of the amino acid residues in a sequence listed above are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue), or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the variant product is fused with another compound, such as a compound to increase the half-life of the protein (for example, polyethylene glycol (PEG)), or a moiety which serves as 20 targeting means to direct the protein to its target tissue or target cell population (such as an antibody), or (iv) one in which additional amino acids are fused to the variant product. Such fragments, variants and derivatives are deemed to be within the scope of those skilled in the art from the teachings herein.

25 A. Preparation of variant product

Recombinant methods for producing and isolating the variant product, and fragments of the protein are described above.

In addition to recombinant production, fragments and portions of variant product may be produced by direct peptide synthesis using solid-phase techniques (cf. Stewart et al., (1969) Solid-Phase Peptide Synthesis, WH Freeman Co, San

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Francisco; Merrifield J., J. Am. Chem. Soc., 85:2149-2154, (1963)). In vitro peptide synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer, Foster City, Calif.) in accordance with 5 the instructions provided by the manufacturer. Fragments of variant product may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Therapeutic uses and compositions utilizing the variant product B.

The variant product of the invention is generally useful in treating diseases and disorders which are characterized by a lower than normal level of variant expression, and or diseases which can be cured or ameliorated by raising the level

of the variant product, even if the level is normal.

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Variant products or fragments may be administered by any of a number of routes and methods designed to provide a consistent and predictable concentration of compound at the target organ or tissue. The product-containing compositions may be administered alone or in combination with other agents, such as stabilizing compounds, and/or in combination with other pharmaceutical 20 agents such as drugs or hormones.

Variant product-containing compositions may be administered by a number of routes including, but not limited to oral, intravenous, intramuscular, transdermal, subcutaneous, topical, sublingual, or rectal means as well as by nasal application. Variant product-containing compositions may also be administered 25 via liposomes. Such administration routes and appropriate formulations are generally known to those of skill in the art.

The product can be given via intravenous or intraperitoneal injection. Similarly, the product may be injected to other localized regions of the body. The product may also be administered via nasal insufflation. Enteral administration is also possible. For such administration, the product should be formulated into an

appropriate capsule or elixir for oral administration, or into a suppository for rectal administration.

The foregoing exemplary administration modes will likely require that the product be formulated into an appropriate carrier, including ointments, gels, suppositories. Appropriate formulations are well known to persons skilled in the art.

Dosage of the product will vary, depending upon the potency and therapeutic index of the particular polypeptide selected.

A therapeutic composition for use in the treatment method can include the product in a sterile injectable solution, the polypeptide in an oral delivery vehicle, the product in an aerosol suitable for nasal administration, or the product in a nebulized form, all prepared according to well known methods. Such compositions comprise a therapeutically effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The product of the invention may also be used to modulate endothelial differentiation and proliferation as well as to modulate apoptosis either ex vivo or in vitro, for example, in cell cultures.

20 Example IV. Screening methods for activators and deactivators (inhibitors)

The present invention also includes an assay for identifying molecules, such as synthetic drugs, antibodies, peptides, or other molecules, which have a modulating effect on the activity of the variant product, e.g. activators or deactivators of the variant product of the present invention. Such an assay comprises the steps of providing an variant product encoded by the nucleic acid sequences of the present invention, contacting the variant protein with one or more candidate molecules to determine the candidate molecules modulating effect on the activity of the variant product, and selecting from the molecules a candidate's molecule capable of modulating variant product physiological activity.

The variant product, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening therapeutic compounds in any of a variety of drug screening techniques. The fragment employed in such a test may be free in solution, affixed to a solid support, borne on a cell membrane or 5 located intracellularly. The formation of binding complexes, between variant product and the agent being tested, may be measured. Alternatively, the activator or deactivator may work by serving as agonist or antagonist, respectively, of the variant receptor, binding entity or target site, and their effect may be determined in connection with any of the above.

Another technique for drug screening which may be used provides for high throughput screening of compounds having suitable binding affinity to the variant product is described in detail by Geysen in PCT Application WO 84/03564, published on Sep. 13, 1984. In summary, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with the full variant product or with fragments of variant product and washed. Bound variant product is then detected by methods well known in the art. Substantially purified variant product can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

Antibodies to the variant product, as described in Example VI below, may also be used in screening assays according to methods well known in the art. For example, a "sandwich" assay may be performed, in which an anti-variant antibody is affixed to a solid surface such as a microtiter plate and variant product is added. Such an assay can be used to capture compounds which bind to the variant product. Alternatively, such an assay may be used to measure the ability of compounds to influence with the binding of variant product to the variant receptor, and then select those compounds which effect the binding.

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Example V. Anti-variant antibodies

A. Synthesis

In still another aspect of the invention, the purified variant product is used to produce anti-variant antibodies which have diagnostic and therapeutic uses related to the activity, distribution, and expression of the variant product.

Antibodies to the variant product may be generated by methods well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, humanized, single chain, Fab fragments and fragments produced by an Fab expression library. Antibodies, i.e., those which inhibit dimer formation, are especially preferred for therapeutic use.

A fragment of the variant product for antibody induction does not require biological activity but have to feature immunological activity; however, the protein fragment or oligopeptide must be antigenic. Peptides used to induce specific antibodies may have an amino acid sequence consisting of at least five amino acids, preferably at least 10 amino acids of the sequences specified in any one of SEQ ID NO: 88 to SEQ ID NO: 174. Preferably they should mimic a portion of the amino acid sequence of the natural protein and may contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of variant protein amino acids may be fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. Procedures well known in the art can be used for the production of antibodies to variant product.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, etc may be immunized by injection with variant product or any portion, fragment or oligopeptide which retains immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet

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hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are potentially useful human adjuvants.

Monoclonal antibodies to variant protein may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include but are not limited to the hybridoma technique originally described by Koehler and Milstein (*Nature* 256:495-497, (1975)), the human B-cell hybridoma technique (Kosbor et al., Immunol. Today 4:72, (1983); Cote et al., Proc. Natl. Acad. Sci. 80:2026-2030, (1983)) and the EBV-hybridoma technique (Cole, et al., Mol. Cell Biol. 62:109-120, (1984)).

Techniques developed for the production of "chimeric antibodies", the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity can also be used (Morrison et al., Proc. Natl. Acad. Sci. 81:6851-6855, (1984); Neuberger et al., Nature 312:604-608, (1984); Takeda et al., Nature 314:452-454, (1985)). Alternatively, techniques described for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce single-chain antibodies specific for the variant protein.

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening recombinant immunoglobulin libraries or panels of highly specific binding reagents as disclosed in Orlandi *et al.* (*Proc. Natl. Acad. Sci.* 86:3833-3837, 1989)), and Winter G and Milstein C., (*Nature* 349:293-299, (1991)).

Antibody fragments which contain specific binding sites for variant protein may also be generated. For example, such fragments include, but are not limited to, the F(ab')₂ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity (Huse W.D. et al., Science 256:1275-1281, (1989)).

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B. Diagnostic applications of antibodies

A variety of protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the formation of complexes between the variant product and its specific antibody and the measurement of complex formation. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two noninterfering epitopes on a specific variant product is preferred, but a competitive binding assay may also be employed. These assays are described in Maddox D.E., et al.,

(J. Exp. Med. 158:1211, (1983)).

Antibodies which specifically bind variant product are useful for the diagnosis of conditions or diseases characterized by expression of the novel variant of the invention (where normally it is not expressed) by over or under expression of variant as well as for detection of diseases in which the proportion between the amount of the variants of the invention and the original sequence from which it varied is altered. Alternatively, such antibodies may be used in assays to monitor patients being treated with variant product, its activators, or its deactivators. Diagnostic assays for variant protein include methods utilizing the antibody and a label to detect variant product in human body fluids or extracts of cells or tissues. The products and antibodies of the present invention may be used with or without modification. Frequently, the proteins and antibodies will be labeled by joining them, either covalently or noncovalently, with a reporter molecule. A wide variety of reporter molecules are known in the art.

A variety of protocols for measuring the variant product, using either polyclonal or monoclonal antibodies specific for the respective protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescent activated cell sorting (FACS). As noted above, a two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on variant product is preferred, but a competitive binding assay may be employed. These assays are

described, among other places, in Maddox, et al. (supra). Such protocols provide a basis for diagnosing altered or abnormal levels of variant product expression.

Normal or standard values for variant product expression are established by combining body fluids or cell extracts taken from normal subjects, preferably human, with antibody to variant product under conditions suitable for complex formation which are well known in the art. The amount of standard complex formation may be quantified by various methods, preferably by photometric methods. Then, standard values obtained from normal samples may be compared with values obtained from samples from subjects potentially affected by disease.

Deviation between standard and subject values establishes the presence of disease state.

The antibody assays are useful to determine the level of variant product present in a body fluid sample, in order to determine whether it is being expressed at all, whether it is being overexpressed or underexpressed in the tissue, or as an indication of how variant levels of variable products are responding to drug treatment.

By another aspect the invention concerns methods for determining the presence or level of various anti-variant antibodies in a biological sample obtained from patients, such as blood or serum sample using as an antigen the variant product. Determination of said antibodies may be indicative to a plurality of pathological conditions or diseases.

C. Therapeutic uses of antibodies

In addition to their diagnostic use the antibodies may have a therapeutical utility in blocking or decreasing the activity of the variant product in pathological conditions where beneficial effect can be achieved by such a decrease.

The antibody employed is preferably a humanized monoclonal antibody, or a human Mab produced by known globulin-gene library methods. The antibody is administered typically as a sterile solution by IV injection, although other parenteral routes may be suitable. Typically, the antibody is administered

in an amount between about 1-15 mg/kg body weight of the subject. Treatment is continued, e.g., with dosing every 1-7 days, until a therapeutic improvement is seen.

Although the invention has been described with reference to specific methods and embodiments, it is appreciated that various modifications and changes may be made without departing from the invention.

Example VI. Expression of ACEV

(a) Immunohistochemical staining:

The immunohistochemical staining was performed using Histostain plus Kit (Zymed Laboratories Inc.). Mouse salivary gland micron sections were prepared using a R. Gung microtome and fixed on superfrost plus slides with 2% Tespa. Deparaffinization was performed in xylene for 10 min. Dehydration was performed three times in absolute ethanol and once 95% ethanol. The slides were washed in DDW and then incubated with 3% H₂O for 5 min. Subsequently, the slide were washed in DDW and twice in 0.05M TrisHCl pH 7.6 (Optimax wash Buffer, BioGenex). The rest of the procedure was performed following the manufacturer's instructions. The results are shown in Figs. 88 and 89.

The immunohistochemical staining was performed on mouse salivary gland micron sections. The immunohistochemestry was done using specific polyclonal antibodies designed against the c-terminus of SEQ ID NO: 144 (12 amino-acids), which are unique to said ACEV product and lack in the original ACE protein (Fig 88-a,b,d magnification X 100; Fig 89-b magnification X 400) compared with the pre-immune rabbit's serum (Fig 88-c, Fig. 89-a).

ACE was found to express in ductal epifilus (Fig 88-a,b,d, Fig 89-b).

The same procedure was repeated for mouse lymph node sectors stained with pre-immune serum (Fig. 90a, 90c – magnifications X 100, X 200, respectively) and immune serum (Fig. 90b and 90c magnifications X 100, X 200 respectively).

The results show positive staining in salivary glands.

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(b) RT - PCR

RNA Purification and cDNA Synthesis Total RNA was extracted from different mouse tissues using Tri-Reagent System (Molecular Research Center, Inc., Cincinnati, OH). Synthesis of first-strand cDNA was carried out using Oligo(dT)15 (Promega, Medison, WI), Superscript II (Gibco/BRL, Gaithersburg, MD), Rnasin (Promega, Medison, WI) and dNTP's (Gibco/BRL, Gaithersburg, MD). + with Superscript II, - without Superscript II.

Polymerase Chain Reaction (PCR): PCR was performed using Expand Long Template PCR system (Roche). As a template cDNA from different tissues was used. The PCR reaction on PTC-225 (MJ Research, Inc.). PCR products were analyzed on an automated DNA sequencer ABI Prizem 310 Genetic Analyzer (Perkin Elmer).

The results are shown in Fig. 91. As can be seen the ACEV of the invention was expressed in skin, lung, heart, thymus, spleen, bone marrow and brain tissue

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CLAIMS:

1. An isolated nucleic acid sequence, of an alternative splicing variant, selected from the group consisting of:

- (i) the nucleic acid sequence depicted in any one of SEQ ID NO: 1 to 5 SEQ ID NO: 87;
 - (ii) nucleic acid sequences having at least 90% identity with the sequence of (i) with the proviso that each sequence is different than the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing; and
- (iii) fragments of (i) or (ii) of at least 20 b.p., provided that said fragment contains a sequence which is not present, as a continuous stretch of nucleotides, in the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing.
- 2. An isolated nucleic acid sequence complementary to the nucleic acid sequence of Claim 1.
 - 3. An amino acid sequence selected from the group consisting of:
 - (i) an amino acid sequence coded by the isolated nucleic acid sequence of alternative splice variants of Claim 1;
- (ii) homologues of the amino acid sequences of (i) in which one or more amino acids has been added, deleted, replaced or chemically modified in the region or adjacent to the region where the amino acid sequences differs from the original amino acid sequence, coded by the original nucleic acid sequence from which the variant has been varied.
- 25 4. An amino acid sequence according to Claim 3, as depicted in any one of SEQ ID NO: 88 to SEQ ID NO: 174.
 - 5. An isolated nucleic acid sequence coding for any one of the amino acid sequences of Claim 3 or 4.
- 6. A purified antibody which binds specifically to any of the amino acid sequence of Claim 3 or 4.

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An expression vector comprising any one of the nucleic acid sequences of 7. Claim 1 or 5 and control elements for the expression of the nucleic acid sequence in a suitable host.

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- An expression vector comprising any one of the nucleic acid sequences of 8. 5 Claim 2, and control elements for the expression of the nucleic acid sequences in a suitable host.
 - A host cell transfected by the expression vector of Claim 7 or 8. 9.
 - A pharmaceutical composition comprising a pharmaceutically acceptable 10. carrier and as an active ingredient an agent selected from the group consisting of:
 - the expression vector of Claim 7; and (i)

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- any one of the amino acid sequences of Claim 3 or 4. (ii)
- A pharmaceutical composition according to Claim 10, for treatment of 11. diseases which can be ameliorated or cured by raising the level of any one of the amino acid sequences depicted in SEQ ID NO: 88 to SEQ ID NO: 174.
- A pharmaceutical composition comprising a pharmaceutically acceptable 15 12. carrier and as an active ingredient an agent selected from the group consisting of:
 - any one of the nucleic acid sequences of Claim 2; (i)
 - the expression vector of Claim 8; and (ii)
 - (iii) the purified antibody of Claim 6.
- A pharmaceutical composition according to Claim 12, for treatment of 13. 20 diseases which can be ameliorated or cured by decreasing the level of any one of the amino acid sequences depicted in SEQ ID NO: 88 to SEQ ID NO: 174.
 - A method for detecting an variant nucleic acid sequence in a biological 14. sample, comprising the steps of:
- hybridizing to nucleic acid material of said biological sample any one (a) 25 of the nucleic acid sequences of Claim 1 or 2; and
 - detecting said hybridization complex;

wherein the presence of said hybridization complex correlates with the presence of an variant nucleic acid sequence in the said biological sample.

A method for determining the level of variant nucleic acid sequences in a biological sample comprising the steps of:

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hybridizing to nucleic acid material of said biological sample any one (a) of the nucleic acid sequences of Claim 1 or 2; and

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- determining the amount of hybridization complexes and normalizing said amount to provide the level of the variant nucleic acid sequences in the 5 sample.
 - A method for determining the ratio between the level of variant of the **16.** nucleic acid sequence in a first biological sample and the level of the original sequence from which the variant has been varied by alternative splicing in a second biological sample comprising:
- (a) determining the level of the variant nucleic acid sequence in the first 10 biological sample according to the method of Claim 15;
 - (b) determining the level of the original sequence in the second biological sample; and
 - (c) comprising the levels obtained in (a) and (b) to give said ratio.
- A method according to Claim 16, wherein said first and said second 17. biological samples are the same sample.
 - A method according to any of Claims 14 to 17, wherein the nucleic acid 18. material of said biological sample are mRNA transcripts.
 - A method according to Claim 18, where the nucleic acid sequence is present 19. in a nucleic acid chip.
 - A method for identifying candidate compounds capable of binding to the 20. variant product and modulating its activity the method comprising:
 - providing any one of the amino acid sequences as defined in Claim 3 (i) or 4:

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- contacting a candidate compound with said amino acid sequence; (ii)
- determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.
- A method according to Claim 20, wherein the compound is an activator and the measured effect is increase in the biological activity.

- A method according to Claim 20, wherein the compound is an deactivator 22. and the effect is decrease in the biological activity.
- An activator of any one of the amino acid sequences of Claim 3 or 4. 23.
- An deactivator of any one of the amino acid sequences of Claims 3 or 4. 24.
- A method for detecting any one of the amino acid sequences of Claim 3 or 4 5 **25**. in a biological sample, comprising the steps of:
 - contacting with said biological sample the antibody of Claim 8, (a) thereby forming an antibody-antigen complex; and
 - detecting said antibody-antigen complex (b)
- wherein the presence of said antibody-antigen complex correlates with the 10 presence of the desired amino acid in said biological sample.
 - A method for detecting the level of the amino acid sequence of any one of 26. Claim 3 or 4 in a biological sample, comprising the steps of:
- contacting with said biological sample the antibody of Claim 8, (a) 15 thereby forming an antibody-antigen complex; and
 - detecting the amount of said antibody-antigen complex and (b) normalizing said amount to provide the level of said amino acid sequence in the sample.
 - A method for determining the ratio between the level of any one of the amino acid sequences of Claims 3 or 4 present in a first biological sample and the level of the original amino acid sequences from which they were varied by alternative splicing, present in a second biological sample, the method comprising:
 - determining the level of the amino acid sequences of Claims 3 or 4 (a) into a first sample by the method of Claim 26;
- determining the level of the original amino acid sequence in the 25 second sample; and
 - comparing the level obtained in (a) and (b) to give said ratio. (c)
 - A method according to Claim 27, wherein said first and said second 28. biological samples are the same sample.
- A method for detecting any one of the antibodies of Claim 6 in a biological sample comprising the steps of:

- (a) contacting said biological sample with any one of the amino acid sequences of Claim 3 or 4 thereby forming an antibody-antigen complex; and
- (b) detecting said antibody-antigen complex
 wherein the presence of said antibody-antigen complex correlates with the
 presence of the antibody in said biological sample.
 - 30. A method for detecting the level of any one of the antibodies of Claim 6 in a biological sample comprising the steps of:
 - (a) contacting said biological sample with any one of the amino acid sequences of Claim 3;
- 10 (b) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the levels of said antibody in the sample.
 - 31. An isolated nucleic acid sequence according to Claim 1 of an alternative splicing variant of an angiotensin converting enzyme (ACEV) selected from the group consisting of:
- 15 (i) the nucleic acid sequence depicted in SEQ ID NO: 57 or SEQ ID NO: 85;
 - (ii) nucleic acid sequences having at least 90% identity with the sequence of (i) with the proviso that each sequence is different than the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing; and
 - (iii) fragments of (i) or (ii) of at least 20 b.p., provided that said fragment contains a sequence which is not present, as a continuous stretch of nucleotides, in the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing.
- 25 32. An isolated nucleic acid sequence complementary to the nucleic acid sequence of Claim 31.
 - 33. An amino acid sequence selected from the group consisting of:
 - (i) an amino acid sequence coded by the isolated nucleic acid sequence of alternative splice variants of Claim 31;
- 30 (ii) homologues of the amino acid sequences of (i) in which one or more amino acids has been added, deleted, replaced or chemically modified in the region

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or adjacent to the region where the amino acid sequences differs from the original amino acid sequence, coded by the original nucleic acid sequence from which the variant has been varied.

- An amino acid sequence according to Claim 33, as depicted in SEQ ID NO: 34. 144 or SEQ ID NO: 172.
- An isolated nucleic acid sequence coding for any one of the amino acid 35. sequences of Claim 33 or 34.
- A purified antibody which binds specifically to any of the amino acid **36.** sequence of Claim 33 or 34.
- An expression vector comprising any one of the nucleic acid sequences of 37. 10 Claim 31 or 35 and control elements for the expression of the nucleic acid sequence in a suitable host.
 - An expression vector comprising any one of the nucleic acid sequences of 38. Claim 32, and control elements for the expression of the nucleic acid sequences in a suitable host.
 - A host cell transfected by the expression vector of Claim 37 or 38. **39.**
 - A pharmaceutical composition comprising a pharmaceutically acceptable 40. carrier and as an active ingredient an agent selected from the group consisting of:
 - the expression vector of Claim 37; and (i)

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- any one of the amino acid sequences of Claim 33 or 34.
- A pharmaceutical composition according to Claim 40, for treatment of 41. diseases which can be ameliorated or cured by raising the level of any one of the amino acid sequences depicted in SEQ ID NO: 144 or SEQ ID NO: 172.
- A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an agent selected from the group consisting of:
 - any one of the nucleic acid sequences of Claim 32; (i)
 - the expression vector of Claim 38; and (ii)
 - the purified antibody of Claim 36. (iii)
- A pharmaceutical composition according to Claim 42, for treatment of diseases which can be ameliorated or cured by decreasing the level of the amino acid sequences depicted in SEQ ID NO: 144 or SEQ ID NO: 172.

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- 44. A pharmaceutical composition according to Claim 40 or 42 for the treatment of a disease selected from: cardiovascular disorders, congestive heart failure, hypertension, renal hypertension, diabetes, multiple sclerosis, sarcoidosis, nonsarcoidotic pulmonary granulomatous diseases, vascular pathologies involving an endothelial abnormality and cancer.
 - 45. A method for detecting an variant nucleic acid sequence in a biological sample, comprising the steps of:
 - (a) hybridizing to nucleic acid material of said biological sample any one of the nucleic acid sequences of Claim 31 or 32; and
 - (b) detecting said hybridization complex;

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wherein the presence of said hybridization complex correlates with the presence of an variant nucleic acid sequence in the said biological sample.

- 46. A method for determining the level of variant nucleic acid sequences in a biological sample comprising the steps of:
- 15 (a) hybridizing to nucleic acid material of said biological sample any one of the nucleic acid sequences of Claim 31 or 32; and
 - (b) determining the amount of hybridization complexes and normalizing said amount to provide the level of the variant nucleic acid sequences in the sample.
- 47. A method for determining the ratio between the level of variant of the nucleic acid sequence in a first biological sample and the level of the original sequence from which the variant has been varied by alternative splicing in a second biological sample comprising:
- (a) determining the level of the variant nucleic acid sequence in the first biological sample according to the method of Claim 46;
 - (b) determining the level of the original sequence in the second biological sample; and
 - (c) comprising the levels obtained in (a) and (b) to give said ratio.
- 48. A method according to Claim 47, wherein said first and said second biological samples are the same sample.

- 49. A method according to any of Claims 45 to 48, wherein the nucleic acid material of said biological sample are mRNA transcripts.
- 50. A method according to Claim 49, where the nucleic acid sequence is present in a nucleic acid chip.
- 5 51. A method for identifying candidate compounds capable of binding to the variant product and modulating its activity the method comprising:
 - (i) providing any one of the amino acid sequences as defined in Claim 33 or 34;
 - (ii) contacting a candidate compound with said amino acid sequence;
- (iii) determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.
 - 52. A method according to Claim 51, wherein the compound is an activator and the measured effect is increase in the biological activity.
- 53. A method according to Claim 51, wherein the compound is an deactivator and the effect is decrease in the biological activity.
 - 54. An activator of any one of the amino acid sequences of Claim 33 or 34.
 - 55. An deactivator of any one of the amino acid sequences of Claims 33 or 34.
 - 56. A method for detecting any one of the amino acid sequences of Claim 33 or 34 in a biological sample, comprising the steps of:
 - (a) contacting with said biological sample the antibody of Claim 38, thereby forming an antibody-antigen complex; and
 - (b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of the desired amino acid in said biological sample.

- 57. A method for detecting the level of the amino acid sequence of any one of Claim 33 or 34 in a biological sample, comprising the steps of:
- (a) contacting with said biological sample the antibody of Claim 38, thereby forming an antibody-antigen complex; and

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- (b) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the level of said amino acid sequence in the sample.
- 58. A method for determining the ratio between the level of any one of the amino acid sequences of Claims 33 or 34 present in a first biological sample and the level of the original amino acid sequences from which they were varied by alternative splicing, present in a second biological sample, the method comprising:
 - (a) determining the level of the amino acid sequences of Claims 33 or 34 into a first sample by the method of Claim 57;
- (b) determining the level of the original amino acid sequence in the second sample; and
 - (c) comparing the level obtained in (a) and (b) to give said ratio.
 - 59. A method according to Claim 58, wherein said first and said second biological samples are the same sample.
- 15 60. A method for detecting any one of the antibodies of Claim 36 in a biological sample comprising the steps of:
 - (a) contacting said biological sample with any one of the amino acid sequences of Claim 3 or 4 thereby forming an antibody-antigen complex; and
 - (b) detecting said antibody-antigen complex wherein the presence of said antibody-antigen complex correlates with the presence of the antibody in said biological sample.
 - 61. A method for detecting the level of any one of the antibodies of Claim 36 in a biological sample comprising the steps of:
- (a) contacting said biological sample with any one of the amino acid sequences of Claim 33;
 - (b) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the levels of said antibody in the sample.

H H	MPIMGSSVYITVELAIAVLAILGNVLVCWAVWLNSNLQNVTNYFVVSLAA 50
51	ADIAVGVLAIPFAITISTGFCAACHGCLFIACFVLVLTQSSIFSLLAIAI 100
51	
101	DRYIAIRIPLRYNGLVTGTRAKGIIAICWVLSFAIGLTPMLGWNNCGQPK 150
101	DRYIAIRIP
151	
151	
201	
7	
201	FLAARRQLK

400	GYALGLVSGGSAQESQGNTGLPDVELLSHELKGVCPEPPGL	\sim
389	340 APHPERRPNGYALGLVSGGSAQESQGNTGLPDVELLSHELKGVCPEPPGL	∞
350	QQEPFKAAGTSARVLAAHGSDGEQVSLRLNGHPPGVWANGS	\sim
339	290 KIIRSHVLRQQEPFKAAGTSARVLAAHGSDGEQVSLRLNGHPPGVWANGS	2
300	251 IINCFTFFCPDCSHAPLWLMYLAIVLSHTNSVVNPFIYAYRIREFRQTFR	2
289		<

DDPLAQDGAGVS 4 401

390

FIG. 1 $(CONT.^{1})$

49 RVLWAPAEAHPLSPQGHPARLHRIVPRLRDVFGWGNLTCPICKGLFTAIN 98 141 LGLKKEPNVARVGSVAIKLCNLLKIAPPAVCQSIVHLFEDDMVEVWRRSV 190	OSCPRSGREQGODGTAGAPGLLWMGLVLALALALALALSDS	1 MPRYGASIRQSCPRSGREQGQDGTAGAPGLLWMGLVLALALALALALSDS 90
•	RVLWAPAEAHPLSPQGHPARLHRIVPRLRDVFGWGNLTCPICKGLFTAIN LGLKKEPNVARVGSVAIKLCNLLKIAPPAVCQSIVHLFEDDMVEVWRRSV	RVLWAPAEAHPLSPQGHPARLHRIVPRLRDVFGWGNLTCPICKGLFTAIN

ILFLTDLHWDHDYLEGTDPDCADPLCCRRGSGLPPASRPGAGYWGEYSKC FIG.

199

241

ILFLTDLHWDHDYLEGTDPDCADPLCCRRGSGLPPASRPGAGYWGEYSKC

290

248

									-
340	298	390	348	440	398	490	448	540	491
DLPLRTLESLLSGLGPAGPFDMVYWTGDIPAHDVWHQTRQDQLRALTTVT		ALVRKFLGPVPVYPAVGNHESTPVNSFPPPFIEGNHSSRWLYEAMAKAWE		PWLPAEAL		•		7	
291	249	341	299	391	349	441	399	491	449

590	495	640	545	069	л Q Л		
541 SLPYPGVGGIGEGGWSQSLQSMGRMCGPSLELPLLLAPPVSPTSLAGYRV 5	492GYRV 4	SSHVVLDHETYILNLTQANIPGAIPHWQLLYRARETYGLPN	496 YQIDGNYSGSSHVVLDHETYILNLTQANIPGAIPHWQLLYRARETYGLPN 5			546 TLPTAWHNLVYRMRGDMQLFQTFWFLYHKGHFFSEFCG1FCKLA1LCAZU	596 SARADSPALCKHLMPUGSDFEAXSDWIN DE SE

FIG. 2 (CONT.²)

	COKGGTCVNMPSGPHCLCFQHLIGNACQKERCFEFQLLRFFHKNEIWYRT CQKGGTCVNMPSGPHCLCPQHLTGNHCQKERCFEFQLLRFFHKNEIWYRT EQAAVARCQCKGPDAHCQRLASQACRTNPCLHGGRCLEVEGHRLCHCPVG
	ARCQCKGPDAHCQRLASQACRTNPCLHGGRCLEVEGHRLCHCPVG
	JARCQCKGPDAHCQRLASQACRTNPCLHGGRCLEVEGHRLCHCPVG
2	
150	COKGGTCVNMPSGPHCLCPQHLTGNHCQKEKCFEPQLLRFFHKNEIWYRT
103	HILLIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
100	THKGRPGPQPWCATTPNFDQDQRWGYCLEPKKVKDHCSKHSP
53	
20	

QARNWGLGGHAFCRNPDNDIRPWCFVLNRDRLSWEYCDLAQCQTPTQAAP 300 	PTPVSPRLHVPLMPAQPAPPKPQPTTRTPPQSQTPGALPAKREQPPSLTR 350	A 40		PCWVLTAAHCLQDRPAPEDLTVVLGQERRNHSCEPCQTLAVRSYRLHEAF 450		SPVSYQHDLALLRLQEDADGSCALLSPYVQPVCLPSGAARPSETTLCQVA 500	
	PTPVSPRLH						
251	301	304	354	401	404	451	454

FIG. 3 $(CONT.^{1})$

GWGHQFEAS 509 |||||||| GWGHQFEGA 512

501

504

1 MARLGNCSLIWAALIILLLPGSLEECGAISVSAFIVALGDFIIASCIIAQ 30
51 NCSHLDPEPQILWRLGAELQPGGRQQRLSDGTQESIITLPHLNHTQAFLS 100
101 CCLNWGNSLQILDQVELRAGYPPAIPHNLSCLMNLTTSSLICQWEPGPET 150
101 CCLNWGNSLQILDQVELRAGYPPAIPHNLSCLMNLTTSSLICQWEPGPET 150
151 HLPTSFTLKSFKSRGNCQTQGDSILDCVPKDGQSHCCIPRKHLLLYQNMG 200
201 IWVQAENALGTSMSPQLCLDPMDVVKLEPPMLRTMDPSPEAAPPQAGCLQ 250
11111111111111111111111111111111111111

251	• •	300
251	LCWEPWQPGLHINQKCELRHKPQRGEASWALVGPLPLEALQYELCGLLPA	300
301	-	320
301		350
321	GAILPLCNTTELSCTFHLP	339
351	TVQLFWKPVPLEEDSGRIQGYVVSWRPSGQAGAILPLCNTTELSCTFHLP	400
340	SEAQEVALVAYNSAGTSRPTPVVFSESRGPALTRLHAMARDPHSLWVGWE	389
401	SEAQEVALVAYNSAGTSRPTPVVFSESRGPALTRLHAMARDPHSLWVGWE	450
390	PPNPWPQGYVIEWGLGPPSASNSNKTWRMEQNGRATGFLLKENIRPFQLY	439
451		200

FIG. 4 (CONT. 1)

440	
501	
490	PPF1,GKSP1,THYTTFWTNAONOSFSAN,TTASAST,NASSRGFV1,HGT,FVATTTYHT,19879,
,	
	CPETONOLINITIEMINAQNQOFOALENASOKGFVENGERASEINITH OO
040	MAASQAGAINSIVLIAMILIPEGSELHIILLGLEGLLLLLICLCGIAWLCC 389
601	MAASQAGA
590	SPNRKNPLWPSVPDPAHSSLGSWVPTIMEEDAFQLPGLGTPPITKLTVLE 639
651	SPNRKNPLWPSVPDPAHSSLGSWVPTIMEEDAFQLPGLGTPPITKLTVLE 700
640	689 VOUSTISOSOGOTSVAGGEOTVATOVITATISOTISSNHSIMAVAXXIOI
) 1	
701	EDEKKPVPWESHNSSETCGLPTLVQTYVLQGDPRAVSTQPQSQSGTSDQV 750

IG. 4 (CONT.²)

775 VTPAPSQEDDCVFGPLLNFPLLQGIRVHGMEALGSF 740

836 VTPAPSQEDDCVFGPLLNFPLLQGIRVHGMEALGSF 801

FIG.4 (CONT.3)

250	201 IWVQAENALGTSMSPQLCLDPMDVVKLEPPMLRTMDPSPEAAPPQAGCLQ	Ž
7		7
007	LKSFKSRGNCQTQGDSILDCVPKDGQSHCCIPKKHLLLYQNMG	,
) (-1
200		-
150	101 CCLNWGNSLQILDQVELRAGYPPAIPHNLSCLMNLTTSSLICQWEPGPET	7
1.50	SLQILDQVELRAGYPPAIPHNLSCLMNLTTSSLICQWEPGPET	1(
100	51 NCSHLDPEPQILWRLGAELQPGGRQQRLSDGTQESIITLPHLNHTQAFLS	Ŋ
100	NCSHLDPEPQILWRLGAELQPGGRQQRLSDGTQESIITLPHLNHTQAFLS	51
20	1 MARLGNCSLTWAALIILLPGSLEECGHISVSAPIVHLGDPITASCIIKQ	
50	MARLGNCSLTWAALIILLLPGSLEECGHISVSAPIVHLGDPITASCIIKQ 5	

FIG. 5 $(CONT.^{1})$

251	LCWEPWQPGLHINQKCELRHKPQRGEASWALVGPLPLEALQYELCGLLPA 300
251	LCWEPWQPGLHINQKCELRHKPQRGEASWALVGPLPLEALQYELCGLLFA 300
301	TAYTLQIRCIRWPLPGHWSDWSPSLELRTTERAPTVRLDTWWRQRQLDPR 350
301	
ר ה	007 d.THATADS.TATTMA.TT.ASAOSSAGAMSXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
100 100	
351	TVQLFWKPVPLEEDSGRIQGYVVSWRPSGQAGAILPLCNTTELSCTFHLP 400
101	
-1 ○ 1*	
401	SEAQEVALVAYNSAGTSRPTPVVFSESRGPALTRLHAMARDPHSLWVGWE 450
451	PPNPWPQG
451	PPNPWPQGYVIEWGLGPPSASNSNKTWRMEQNGRATGFLLKENIRPFQLY 500

713	4 DPAHSSLGSWVPTIMEEDAFOLPGLGTPPITKLTVLEEDEKKPVPWESHN	664
750		701
663		614
700	LTLMTLT	651
613	SAILNASSRGFVLHGLEPASLYHIHLMAASQAGATNSTV SAILNASSRGFVLHGLEPASLYHIHLMAASQAGATNSTV	575
650	IQAYADRTPLP	601
574		551
009	PPELGKSPLTHYTIFWTNAQNQSFCESXLSSPTAPEGLEGGAQLPRRXFT	551
550		501
550	EIIVTPLYQDTMGPSQHVYAYSQEMAPSHAPELHLKHIGKTWAQLEWVPE	501

FIG. 5 $(CONT.^3)$

⊣	MQKIMHISVLLSPVLWGLIFGVSSNSIQIGGLFPRGADQEYSAFRVGMVQ 50
[]	MOKIMHISVLLSPVLWGLIFGVSSNSIQIGGLFPRGADQEYSAFRVGMVQ 50
51	_ դ
51	FSTSEFRLTPHIDNLEVANSFAVTNAFCSQFSRGVYAIFGFYDKKSVNTI 100
101	TSECGTLHV
101	TSFCGTLHVSFITPSFPTDGTHPFVIQMRPDLKGALLSLIEYYQWDKFAY 150
151	TYDSDRGLS
151	
201	LKKERRVIL
201	

OFGGANVSGFQIVDYDDSLVSKFIERWSTLEEKEYPGAHTTTIKYTSALT	300
	300
	350
	350
	400
	400
	450
	450
251 251 301 301 351 401	QFGGANVSGFQIVDYDDSLVSKFIERWSTLEEKEYPGAHTTTIKYTSALT

FIG. 6 (CONT. 1)

451	AEIAKHCGFKYKLTIVGDGKYGARDADTKIWNGMVGELVYGKADIAIAPL 500
451	AEIAKHCGFKYKLTIVGDGKYGARDADTKIWNGMVGELVYGKADIAIAPL 500
501	TITLVREE
501	TITLVREEVIDFSKPFMSLGISIMIKKPQKSKPGVFSFLDPLAYEIWMCI 550
551	VFAYIGVSVVLFLVSRFSPYEWHTEEFEDGRETQSSESTNEFGIFNSLWF 600
551	VFAYIGVSVVLFLVSRFSPYEWHTEEFEDGRETQSSESTNEFGIFNSLWF 600
601	SLGAFMRQGCDISPRSLSGRIVGGVWWFFTLIIISSYTANLAAFLTVERM 650
601	SLGAFMRQGCDISPRSLSGRIVGGVWWFFTLIIISSYTANLAAFLTVERM 650
651	VSPIESAEDLSKQTEIAYGTLDSGSTKEFFRRSKIAVFDKMWTYMRSAEP 700
651	VSPIESAEDLSKQTEIAYGTLDSGSTKEFFRRSKIAVFDKMWTYMRSAEP 700

FIG. 6 (CONT.²)

795

KGYGIATPKGSSLGTPVNLAVLKLSEQGVLDKLKNKWWYDKGECG

FIG. 6 (CONT. 3)

751

	127 FSDEMNTISDNLAARDFINWLIQTKITDRK 156
150	: 101 GTFTSDVSSYLEGQAAKEFIAWLVKGRGRRDFPEEVAIVEELGRRHADGS
126	
100	
100	51 KRHSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNNIAKRHDEFERHAE
50	
50	1 MKSIYFVAGLFVMLVQGSWQRSLQDTEEKSRSFSASQADPLSDPDQMNED

FIG.

	9	6 SGTARKTLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKVTIRLFQQ 55	
	129		
	56		
	179	179 QKHPQGSLDTGEEAEEVGLKGERSELLLSEKVVDARKSTWHVFPVSSSIQ 228	
	106		
• •	229	229 RLLDQGKSSLDVRIACEQCQESGASLVLLGKKKKKEEEGEGKKKGGGEGG 278	
	156	156 AGADEEKEQSHRPFLMLQARQSEDHPHRRRRRGLECDGKVNICCKKQFFV 205	
- 3	279	279 AGADEEKEQSHRPFLMLQARQSEDHPHRRRRRGLECDGKVNICCKKQFFV 328	

FIG.

FIG. 8 $(CONT.^{1})$

	I MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEDSKDVAAPHRQPL1SS 50
\leftarrow	
51	ERIDKQIRYILDGISALRKETCNXSNMC
51	
0	
0	CFQSGFNEETCHVALLIGHEFFVILEILQNAFESSEEQARAVQMSINVI
101	
133	IQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKE 182
151	IQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKE 200
	183 FLQSSLRALRQM 194

g

FLOSSLRALROM

201

⊣ .	MNSFST	9
⊷	MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPFGEDSKDVAAFHKQFL155 5	00
7	TCNKSNMCESSKEALAENNLNLPKMAEKDG 3	36
51	ERIDKQIRYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDG	100
37	CFQSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVL	98
101		150
87	IQFLQKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTTHLILRSFKE	136
151		200
	OV L MODIFICATION TO	

201

~~	MPRLFLFHLLEFCLLLNQFSRAVAAKWKDDVIKLCGRELVRAQIAICGMS 50	
Н		
51	TWSKRSLSQEDAPQTPRPVAAGDFIQTVSLGISPDGGKALRTGSCFTREF 100	
51	TWSKRSLSQEDAPQTPRPVA70	
101	LGALSKLVPSFINKDTETIIIMLEFIANLPPELKAALSERQPSLPELQQY 150	
71	.:	_
151	VPALKDSS	
116		

FIG. 11

50 50 MKLCVTVLSLLMLVAAFCSPALSAPMGSDPPTACCFSYTARKLPRNFVVD MKLCVTVLSLLMLVAAFCSPALSAPMGSDPPTACCFSYTARKLPRNFVVD 92 87 YYETSSLCSQPAVV....GKQVCADPSESWVQEYVYDLELN YYETSSLCSQPAVVFQTKRSKQVCADPSESWVQEYVYDLELN 51

FIG. 12

 1	MGLAWGLGVLFLMHVCGTNRIPESGGDNSVFDIFELTGAARKGSGRRLVK 50	
· —	MGLAWGLGVLFLMHVCGTNRIPESGGDNSVFDIFELTGAARKGSGRRLVK 50	
51	GPDPSSPAFRIEDANLIPPVPDDKFQDLVDAVRAEKGFLLLASLRQMKKT 100	
51		
101	101 RGTLLALERKDHSGQVFSVVSNGKAGTLDLSLTVQGKQHVVSVEEALLAT 150	
101		
151	GQWKSITL	
151	GOWKSITLFVQEDRAQLYIDCEKMENAELDVPIQSVFTRDLASIARLRIA 200	
201		
201		

13 (CONT.¹)

251	SPAIRTNYIGHKTKDLQAICGISCDELSSMVLELRGLRTIVTTLQDSIRK	300
251		300
301	VTEENKELANELRRPPLCYHNĠVQYRNNEEWTVDSCTECHCQNSVTICKK	350
301		350
351	VSCPIMPCSNATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIO	400
351	VSCPTMPCSNATVPDGECGPRCMPSDSADDGWSPWSEWTSCSTSCGNGTO	400
107	TASAS MASMASMASAAAAAAAAAAAAAAAAAAAAAAAAA	. С
⊣ > r)) #
401	QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRFKQDGGWSHWSPWSSCSVT	450
451	. CGDGVITRIRLCNSPSPOMNGKPCEGEARETKACKKDACPINGGWGPWSP	500
451	CGDGVITRIRLCNSPSPQMNGKPCEGEARETKACKKDACPINGGWGPWSP	500

501	WDICSVTCGGGVQKRSRLCNNPTPQFGGKDCVGDVTENQICNKQDCPIDG 550	550
501		550
551	CLSNPCFAGVKCTSYPDGSWKČGACPPGYSGNGIQCTDVDECKEVPDACF	009
551		009
601	601 NHNGEHRCENTDPGYNCLPCPPRFTGSQPFGQGVEHATANKQVCKPRNPC	650
601	NHNGEHRCENTDPGYNCLPCPPRFTGSQPFGQGVEHATANKQVCKPRNPC	650
651		700
651		700

FIG. 13 (CONT.²)

722

701

701

П	MGLAWGLGVLFLMHVCGTNRIPESGGDNSVFDIFELTGAARKGSGRRLVK	50
, 		50
51	GPDPSSPAFRIEDANLIPPVPDDKFQDLVDAVRAEKGFLLLASLRQMKKT	100
51	GPDPSSPAFRIEDANLIPPVPDDKFQDLVDAVRTEKGFLLLASLRQMKKT	100
101	RGTI,I,AI,FRKDHSGOVFSVVSNGKAGTI,DI,SI,TVOGKOHVVSVFFAI,I,AT	150
)
101	RGTLLALERKDHSGQVFSVVSNGKAGTLDLSLTVQGKQHVVSVEEALLAT	150
151	GOWKSITLFVQEDRAQLYIDCEKMENAELDVPIQSVFTRDLASIARLRIA	200
151	GOWKSITLFVQEDRAQLYIDCEKMENAELDVPIQSVFTRDLASIARLRIA	200
201	KGGVNDNFQGVLQNVRFVFGTTPEDILRNKGCSSSTSVLLTLDNNVVNGS	250
		-
201	KGGVNDNFQGVLQNVRFVFGTTPEDILRNKGCSSSTSVLLTLDNNVVNGS	250

FIG. 14 (CONT.¹)

251	SPAIRTNYIGHKTKDLQAICGISCDELSSMVLELRGLRTIVTTLQDSIRK 300
251	SPAIRTNYIGHKTKDLOAICGISCDELSSMVLELRGLRTIVTTLQDSIRK 300
l)]	
301	VTEENKELANELRRPPLCYHNGVQYRNNEEWTVDSCTECHCQNSVTICKK 350
	1
301	VTEENKELANELRRPPLCYHNGVQYRNNEEWTVDSCTECHCQNSVTICKK 350
351	VSCPIMPCSNATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIQ 400
•	
351	VSCPIMPCSNATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIQ 400
401	QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRFKQDGGWSHWSPWSSCSVT 450
401	QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRFKQDGGWSHWSPWSSCSVT 450
451	CGDGVITR
451	CGDGVITRIRLCNSPSPQMNGKPCEGEARETKACKKDACPINGGWGPWSP 500

FIG. 14 (CONT.²)

H	~	0
\leftarrow	MGLAWGLGVLFLMHVCGTNRIPESGGDNSVFDIFELTGAARKGSGRRLVK 50	0
η -		,
7	GFDFSSFAFKIEDANLIFFVFDDKFQDLVDAVRAEKGFLLLASLRQMKKT 10	100
51	GPDPSSPAFRIEDANLIPPVPDDKFQDLVDAVRTEKGFLLLASLRQMKKT 100	0.0
101	RGTLLALERKDHSGOVFSVVSNGKAGTI DI SI TVOCKOHVVSVFTA I I A A	ر ر
101	RGTLLALERKDHSGQVFSVVSNGKAGTLDLSLTVQGKQHVVSVEEALLAT	150
ר ת		
T C T	GOWASIILE VOEDRAQLIIOCERMENAELDVPIOSVFTRDLASIARLRIA	200
151	GOWKSITLFVQEDRAQLYIDCEKMENAELDVPIQSVFTRDLASIARLRIA	200
201	KGGVNDNFQGVLQNVRFVFGTTPEDILRNKGCSSSTSVLLTLDNNVVNGS	250
201	KGGVNDNFQGVLQNVRFVFGTTPEDILRNKGCSSSTSVLLTLDNNVVNGS 2	250

FIG. 15 (CONT.¹)

107	SFAIKINIIGHKIKDLQAICGISCDELSSMVLELRGLRTIVTTLQDSIRK 300
251	SPAIRTNYIGHKTKDLQAICGISCDELSSMVLELRGLRTIVTTLQDSIRK 300
301	7
, ()	
30T	VTEENKELANELRRPPLCYHNGVQYRNNEEWTVDSCTECHCQNSVTICKK 350
351	VSCPIMPCSNATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIO 400
351	VSCPIMPCSNATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIQ 400
401	QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRFKQDGGWSHWSPWSSCSVT 450
401	QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRFKQDGGWSHWSPWSSCSVT 450
)
	451 CGDGVITRIRLCNSPSPQMNGKPCEGEARETKACKKDACP 490
	i
•	451 CGDGVITRIRLCNSPSPOMNGKPCEGEARETKACKKDACP 490

-	MGLAWGLGVLFLMHVCGTNRIPESGGDNSVFDIFELTGAARKGSGRRLVK 50
	MGLAWGLG
51	\odot
51	GPDPSSPAFRIEDANLIPPVPDDKFQDLVDAVRTEKGFLLLASLRQMKKT 100
101	RGTLLALE
101	
151	GOWKSTTT TO A CONTRACT TO A CONTRACT TO A SOUTH TO THE SOUTH TO A SOUTH TO THE SOUT
) 	
151	GQWKSITL
0	
T07	•
201	
T O 7	AGGVNDNFQGVLQNVRFVFGTTPEDILRNKGCSSSTSVLLTLDNNVVNGS 250

251	SPAIRTNYIGHKTKDLQAICGISCDELSSMVLELRGLRTIVTTLQDSIRK	300
251		300
301		350
301	VTEENKELANELRRPPLCYHNGVQYRNNEEWTVDSCTECHCQNSVTICKK	350
351		400
351	NATVPDGECCPRCWPSDSADDGWSPWSEWTSCSTSCGNGIQ	400
	401 QRGRSCDSLNNRCEGSSVQTRTCHIQECDKRCKHLSLSGTW 441	

FIG.

1 MAALMTPGTGAPPAPGDFSGEGSQGLPDPSPEPKQLPELIRMKRDGGRLS	LPELIRMKRDGGRLS 50
1 MAALMTPGTGAPPAPGDFSGEGSQGLPDPSPEPKQLPELIRMKRDGGRLS	LPELIRMKRDGGRLS 50
51 EADIRGFVAAVVNGSAQGAQIGAMLMAIRLRGMDLEETSVLTQALAQSGQ	EETSVLTQALAQSGQ 100
51 EADIRGFVAAVVNGSAQGAQIGAMLMAIRLRGMDLEETSVLTQALAQSGQ	FILLITOALAOSGO 100
101 QLEWPEAWRQQLVDKHSTGGVGDKVSLVLAPALAACGCKVPMISGRGLGH	CGCKVPMISGRGLGH 150
101 OLEMPEAMROOLVINKHSTECTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOTOT	
	CGCKVPMISGRGLGH 150
151 TGGTLDKLESIPGFNVIQSPEQMQVLLDQAGCCIVGQSEQLVPADGILYA 200	GOSEQLVPADGILYA 200
151 TGGTLDKLESIPGFNVIQSPEQMQVLLDQAGCCIVGQSEQLVPADGILYA	
AKDVIAIVDS	FGGAAVFPNQEQARE 250
201 ARDVTATVDSI, PI, TTASTI, SKRI MEGI SATIMANIA	
	GGAAVEPNOEOARF 250

17 (CONT. 1) FIG.

1 MAALMTPGTGAPPAPGDFSGEGSQGLPDPSPEPKQLPELIRMKRDGGRLS 50
51 EADIRGFVAAVVNGSAQGAQIGAMLMAIRLRGMDLEETSVLTQALAQSGQ 100
101 QLEWPEAWRQQLVDKHSTGGVGDKVSLVLAPALAACGCKVPMISGRGLGH 150
101 QLEWPEAWRQQLVDKHSTGGVGDKVSLVLAPALAACGCKVPMISGRGLGH 150
151 TGGTLDKLESIPGFNVIQSPEQMQVLLDQAGCCIVGQSEQLVPADGILYA 200
151 TGGTLDKLESIPGFNVIQSPEQMQVLLDQAGCCIVGQSEQLVPADGILYA 200
201 ARDVTATVDSLPLITGWRG.SQPR 223
201 ARDVTATVDSLPLITASILSKKLVEGLSALVVDVKF.GGAAVFPNQEQAR 249

442

482

410

450

224		
250 ELA		
260 PD	260 PDLRDLVTTLGGALLWLSGHAGTQAQGAARVAAALDDGSALGRFERMLAA 309	
300 PD		
310 QG	OGVDPGLARALCSGSPAERRQLLPRAREQEELLAPADGTVELVRALPLAL 359	
350 QG	GGVDPGLARALCSGSPAERRQLLPRAREQEELLAPADGTVELVRALPLAL 399	
360 77	VI HELGAGESRAGEPI, RLGVGAELLVDVGORLRRGTPWLRVHRDGPALSG 409	
AND VI.	400 VIHELGAGRSRAGFPIRLGVGAELLVDVGORLRRGTPWLKVHKUGPALSG 449	

FIG. 18 (CONT.¹)

ידה ידי

225RVAAALTAMDKPLGRCVGHALEVEEALLCMDGAGPP 260
251 LAKTLVGVGASLGLRVAAALTAMDKPLGRCVGHALEVEEALLCMDGAGPP 300
261 DLRDLVTTLGGALLWLSGHAGŤQAQGAARVAAA293

FIG. 19 (CONT. 1)

451

294

1 MASRLTLLTLLLLLAGDRASSNPNATSS
MASKLILLILLILLINGONASONINIIOSSASSASSASSASSASSASSASSASSASSASSASSASSA
32 SKMLFVEPILEVSSLPTTNSTTNSATKITANTTDEPTTQPTTQPTI 81
51 SKMLFVEPILEVSSLPTTNSTTNSATKITANTIDEFILGFILGFILGFILGFILGFILGFILGFILGFILGFILG
82 OPTOPTTOLPTDSPTOPTTGSFCPGPVTLCSDLESHSTEAVLGDALVDFS 131
101 QPTQPTTQLPTDSPTQPTTGSFCPGPVTLCSULESHSTEAVLGDALVDES 130
132 LKLYHAFSAMKKVETNMAFSPFSIASLLTQVLLGAGENTKTNLESILSYP 181
151 LKLYHAFSAMKKVETNMAFSPFSIASLLTQVLLGAGENTKTNLESILSYP 200
189 KNETTUHOALKGFTTKGVTSVSOIFHSPDLAIRDTFVNASRTLYSSSPRV 231
201 KDFTCVHQALKGFTTKGVTSVSQIFHSPDLAIKDIFVNASKILISSSFKV 230

FIG. 2(

FIG. 20 (CONT. 1)

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232	LSNNSDANLELINTWVAKNTNNKISRLLDSLPSDTKLVLLNAITLSAKWK 201
251	LSNNSDANLELINTWVAKNTNNKISRLLDSLPSDTRLVLLNAIYLSAKWK 300
(188 PTO TOPINA THOUTEU KNOVYNOKINAGYSTESSESSESSESSESSESSESSESSESSESSESSESSES
282	TTFUPKKTKMEFFHFKNSVIKVFMMNSKAIFVAMFILDKILMKAKVCKMKNSSST
301	TTFDPKKTRMEPFHFKNSVIKVPMMNSKKYPVAHFIDQTLKAKVGQLQLS 350
332	
351	HNLSLVILVPQNLKHRLEDMEQALSPSVFKAIMEKLEMSKFQFTLLTLFK 400
382	
401	IKVTTSQDMLSIMEKLEFFDFSYDLNLCGLTEDPDLQVSAMQHQTVLELT 450
432	ETGVEAAAA
451	ETGVEAAAASAISVARTLLVFEVQQPFLFVLWDQQHKFPVFMGRVYDPRA 500

116

376

HSKTNGILFCGRFSSP | |||||||||||| HRKTNGILFCGRFSSP

101

361

1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVIMGAKGNIA		00
		20
51 AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC	0 -	100
51 AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC	U	100
101 DFLSSFRDSCOKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	WVAEKTEGKIAELL	150
101 DFLSSFRDSCQKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	WVAEKTEGKIAELL	150
151 SPGSVDPLTRLVLVNAVYFRGNWDEQFDKENTEERLFKVSKNEEKPVQMM	FKVSKNEEKPVQMM	200
		200
) R O
201 FKOSTFKKTYIGEIFTOILVLPYVGKELNMIIMLFULIIULKIVENELII 		
201 FKQSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY	ETTDLRTVEKELTY	250

251	EKFVEWTRLDMMDEEEV	27
251		00
268		33
301		0.0
	294 ADHPFLFFIQHSKTNGILFCGRFSSP 319	
	351 ADHDELEFICHRKTNGILFCGRESSP 376	

FIG. 22 (CONT.¹)

~ 근	MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 50
51	AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLR89
51	
90	
251	HILLILLINDEEEVEVEVSLPRFKLEESYDMESVLRNLGMTDAFELGKA 300
ر. د	PESCMSOTH ST SKWYHKSFWFWFFGTFAAAATAAIMMMRCARFVPRFC 162
) - -	
301	
	163 ADHPFLFFIOHSKTNGILFCGRFSSP 188
	351 ADHPFLFFIQHRKTNGILFCGRFSSP 376

TG. 23

50

50

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MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 55 55 51 AQMAQ

51 AQMAQ

	MHKTASQRLFPGPSYQNIKSIMEDSTILSDWTNSNKQKMKYDFSCELYRM 50
⊣	HILLIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
51	, , ,
7,	STYSTEPAGVPVSERSLARAGEYYTGVNDKVKCECGTMIDNWKIGDSPI 100
H)	
101	OKHKOLYPSCSFIONLVSASLGSTSKNTSPMRNSFAHSLSPTLEHSSLFS 150
101	QKHKQLYPSCSFIQNLVSASLGSTSKNTSPMRNSFAHSLSPTLEHSSLFS 150
151	GSYSSLSP
151	GSYSSLSPNPLNSRAVEDISSSRTNPYSYAMSTEEARFLTYHMWPLTFLS 200
201	
201	PSELARAGFYYIGPGDRVACFACGGKLSNWEPKDDAMSEHRRHFPNCPFL 250
251	ENSLETLR
251	FNSLFTLRFSISNI,SMOTHAARMRTFMYWPSSVPVOPEOLASAGFYYVGR 300

359

333

251

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ADELGEVIKDDIWPNPLQYYLVPDMDDEEGEGEEDDDDDEEEEGLEDIDE 332	ADELGEVIKD	283	
•	•		
PSSKSTEIKWKSGKDLTKRSSQTQNKASRKRQHEEPESFFTWFTDHSDAG 200	PSSKSTEIKW	151	
PSSKSTEIKWKSGKDLTKRSSQTQNKASRKRQHEEPESFFTWFTDHSDAG 282	PSSKSTEIKW	233	
\sim	EEALHYLTRV	101	
EEALHYLTRVEVTEFEDIKSGYRIDFYFDENPYFENKVLSKEFHLNESGD 232	EEALHYLTRV	183	
SQKYNKLRQPFFQKRSELIAKIPNFWVTTFVNHPQVSALLGEED 100	EEILKVEQKY	27	
133 EEILKVEQKYNKLRQPFFQKRSELIAKIPNFWVTTFVNHPQVSALLGEED 182	EEILKVEQKY	133	
MSAPAAKVSKKELNSNHDGADETSEKEQQEAIEHIDEVQNEIDRLNEQAS 50	MSAPAAKVSKI		
Η .)	
83 MSAPAAKVSKKELNSNHDGADETSEKEQQEAIEHIDEVQNEIDRLNEQAS 132	MSAPAAKVSKI	m œ	

┍╌┤	MSAPAAKVSKKELNSNHDGADETSEKEQQEAIEHIDEVQNEIDRLNEQAS 5	20
Н	KKELNSNHDGADETSEKEQQEAIEHIDEVQNEIDRLNEQAS	50
51	EEILKVEQKYNKLRQPFFQKRSELIAKIPNFWVTTFVNHPQVSALLGEED	100
51	EEILKVEQKYNKLRQPFFQKRSELIAKIPNFWVTTFVNHPQVSALLGEED	100
101	EEALHYLTRVEVTEFEDIKSGYRIDFYFDENPYFENKVLSKEFHLNESGD	150
101	EEALHYLTRVEVTEFEDIKSGYRIDFYFDENPYFENKVLSKEFHLNESGD	150
151	PSSKSTEIKWKSGKDLTKRSSQTQNKASRKRQHEEPESFFTWFTDHSDAG	200
151		200
201	ADELGEVIKDDIWPNPLQYYLVPDMDDEEGEGEEDDDDDEEEEGLEDIDE	250
201	ADELGEVIKDDIWPNPLQYYLVPDMDDEEGEGEEDDDDDEEEGLEDIDE	250

FIG. 27

251

121 MSDASLRSTSTMERLVARGTFPVLVRTSACRSLFGPVDHEELSRELQARL 170
171 AELNAEDQNRWDYDFQQDMPLRGPGRLQWTEVDSDSVPAFYRETVQI 217
51 AELNAEDQNRWDYDFQQDMPLRGPGRLQWTEVDSDSVPAFYRETVQVGRC 100
Z18FFAKKKKSAFEKSSGDVFAFCFSFSA Z43
251 AAGTAAASANGAAIKKLSGPLISDFFAKRKRSAPEKSSGDVPAPCPSPSA 300
•
244 APGVGSVEQTPRKRLR 279
301 APGVGSVEQTPRKRLR 316

کا ، کا ،	Z MTLKHLPFILLILSGELYAEEKQCDFPTVENGRIAQYYYTFKSFYFPMS 51
~	MTLRHLPFILLILSGELYAEEKQCDFPTVENGRIAQYYYTFKSFYFPMS 50
52 V	VDKKLSFFCLAGYATESGKQEEQIRCTAEGWSPNPRCYKKCLKPDLRNGY 101
51 V	VDKKLSFFCLAGYATESGKQEEQIRCTAEGWSPNPRCYKKCLKPDLRNGY 100
102	VSNDKVLYKLQERMSYGCSSGYKTTGGKDEEVVHCLSAGWSSQPSCRKEQ 151
101	VSNDKVLYKLQERMSYGCSSGYKTTGGKDEEVVHCLSAGWSSQPSCRKEQ 150
152 I	ETCLAPELEHGNYSTTQRTFKVKDIVAYTCTAGYYTTTGKQTGEAECOAN 201
151 E	ETCLAPELEHGNYSTTQRTFKVKDIVAYTCTAGYYTTTGKQTGEAECQAN 200
	•
202	GWSLTPQCNKLMCSSLRLIENGYFHPVKQTYEEGDVVQFFCHENYYLSGS 251
!	
201 (GWSLTPQCNKLMCSSLRLIENGYFHPVKQTYEEGDLVQFFCHENYYLSGS 250

FIG. 29 (CONT.¹)

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252		
251	DLIQCYNFGWYPESPICEGRRNRCPPPVPLNSKIQPHSTTYRHGERVHI 300	
302		
301	ECELNFVIQGSEELLCENGKWTEPPKCIEEKEKVACEQPPSVENGVAHPH 350	_
352	SEIYYSGDK	
351	SEIYYSGDKVTYRCGGGYSLRGSSTITCNRGRWTLPPECVENIENCKPPP 400	_
402	DIANGVVVD	
401		
452	LEPCTIDVD	
451	LEPCTIDVDHMNRNNIQLKWKYEGKILHGDLIDFVCKQGYNLSPSIPLSE 500	

551

FIG. 29 $(CONT.^2)$

LLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG	50
	50
	99
	100
•	
	109
Ω	750
_	159
751 CLYRNGGCEHICQESLGTARCLCREGFVKAWDGKMCLPQDYPILSGENAD	800

FIG. 3(

FIG. 30 (CONT. 1)

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160	田 -	209
801	LSKEVTSLSNSTQAEVPDDDGTESSTLVAEIMVSGMNYEDDCGPGGCGSH	850
210	,	259
851		006
260	•	309
901	GYVCRCSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR	950
310		359
951	PSSPGRSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE	1000
360	SI,DSYTCNCVIGYSGDRCQTRDLRWWELRHAGYGQKHDIMVVAVCMVALV	409
5 0 0 1		1050
1 O O T		

SSGPDSSSGAAVASC 459		SLQLGSVHLTSWRQK 509			PVGPEKLHSLQSANG 559		
410 LLLLLGMWGTYYYRTRKQLSNPPKNPCDEPSGSVSSSGPDSSSGAAVASC 459		A 60 POPWFVVLEKHODPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK	NO MODE TIME OF TO TO TO TO TO TO THE PARTY OF THE PARTY	PQPWFVVLEKHQDPKNGSLPADGTNGAVVDAGLSFSLQLGSVALISWNQN	510 PHIDGMGTGOSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG		1151 PHIDGMGTGOSCWIPPSSDRGPQEIEGNSHLFSIRFVGFERLDGAMO
410	1051	460) "	1101	71) H	1151

FIG. 30 (CONT.²)

560

1201

TCAG 50	WVDV 100		PGADP 109	 PGADP 750		GENAD 133	GENAD 800	
1 MPWGRRPTWLLLAFLLVFLKISILSVIAWQTGNCQPGPLERSERSGTCAG 1 MPWGRRPTWLLLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG 51 PAPFLVFSQGKSISRI	11111111111111111111111111111111111111	•	67 WAIPSVIRVNKRTGQNRVRLQGSMLKPSSLVVVHPLAKPGADP		· · · · · · · · · · · · · · · · · · ·	110 CLYRNGGCEHICQESLGTARCLCREGFVKAWDGKMCLPQDYP1LSGENAD		751 CLYRNGGCEHICQESLGTARCLCREGEVRAWDGMTCHERFERT

ig. 31

160 LSKEV 801 LSKEV 851 ARCV 901 GYVC 901 GYVC 951 PS	LSKEVTSLSNSTQAEVPDDDGTESSTLVAEIMVSGMNYEDDCGPGGCGSH 209 	ARCVSDGETAECOCLKGFARDGNLCSDIDECVLARSDCPSTSSRCINTEG 259	. ACSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR 309	PSSPGLSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE 359
			260 GYVCRCSEG 11111111 901 GYVCRCSEG	P - 1

FIG. 31 $(CONT.^{1})$

FIG. 31 (CONT.²)

62/209

51

51

110

751

701

29

•	MFWGKKFTWLLAFLLLV
П	HILLILLILLITILLI HPWGRRPTWLLLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG 50
	•
	•
18	•
82	851 ARCVSDGETAECQCLKGFARDGNLCSDIDECVLARSDCPSTSSRCINTEG 900
9	60 GYVCRCSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR 109
06	901 GYVCRCSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR 950
110	
951	PSSPGRSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE 1000

			6	5/209	9	
209	259	1100	309	1150	359	1200
SLDSYTCNCVIGYSGDRCQTRDLRWWELRHAGYGQKHDIMVVAVCMVALV 		LLLLLGMWGTY	260 PQPWFVVLEKHQDPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK	1 POPWFVVLEKHODPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK	310 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG	1151 PHIDGMGTGOSCWIPPSSDRGPOEIEGNSHLPSYRPVGPEKLHSLOSANG
160	210	1051	2(1101	, m	7

FIG. 33 (CONT.¹)

1201

360

				6	66/20	19		
\mathcal{L}	20		27	800	77	850	127	006
1 MTWGK	MPWGRRPTWLLLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG		6 KAWDGKMCLPQDYPILSGENAD	751 CLYRNGGCEHICQESLGTARCLCREGFVKAWDGKMCLPQDYPILSGENAD		801 LSKEVTSLSNSTQAEVPDDDGTESSTLVAEIMVSGMNYEDDCGPGGCGSH		851 ARCVSDGETAECQCLKGFARDGNLCSDIDECVLARSDCPSTSSRCINTEG
	τ-¬			7		∞	·	∞

				67	/209				
177	950	227	1000	277	1050	327	1100	377	1150
_			PSSPGRSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE	-	1 SLDSYTCNCVIGYSGDRCQTRDLRWWELRHAGYGQKHDIMVVAVCMVALV		1 LLLLLGMWGTYYYRTRKQLSNPPKNPCDEPSGSVSSSGPDSSSGAAVASC		
128	901	178	951	228	1001	278	1051	328	1101

FIG. 34 (CONT.¹)

1200 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG 378 1151

428 SCHERAPDLPRQTEPVQ 444

SCHERAPDLPRQTEPVK 1217

1201

FIG. 34 (CONT.²)

386 50 MFRELNEALELKDAHATEESGDSRÅHSSYLKTKKGQSTSRHKKTMVKKVG

1 PDSD 54

387 PDSD 390

-1	MAIFVWFRISASLQPVVDSRHLTVATLEERPFVIVESPDPGTGGCVPNTV 50
382	382 MKYPVWPRYSASLQPVVDSRHLTVATLEERPFVIVESPDPGTGGCVPNTV 431
51	Щ
432	
101	KHGKRVRGV
482	
151	SVMVARSNGTVSPSAFLEPYSPAVWVMMFVMCLTVVATTVFMFFYFFYFT
532	SVMVARSNGTVSPSAFLEPYSPAVWVMMFVMCLTVVAITVFMFFYFSPVS
()
T 0 7	INCNLTRGKKSGGPAFTIGKSVWLLWALVFNNSVPIENPRGTTSKIMVLV 250
582	

251	WAFFAVIFLASYTANLAAFMIQEQYIDTVSGLSDKKFQRPQDQYPPFRFG	300
632	_	681
301	TVPNGSTERNIRSNYRDMHTHMVKFNQRSVEDALTSLKMGKLDAFIYDAA	350
682		731
351	VLNYMAGKDEGCKLVTIGSGKVFATTGYGIAMQKDSHWKRAIDLALLQFL	400
732	VLNYMAGKD	781
401	GDGETQKLETVWLSGICQNEKNEVMSSKLDIDNMAGVFYMLLVAMGLALL	450
782	<u> </u>	831
451	VFAWEHLVYWKLRHSVPNSSQLDFLLAFSRGIYSCFSGVQSLASPPRQAS	500
832	VFAWEHLVY	881

FIG. 36 (CONT.⁺)

550	600	650	700	750
PDLTASSAQASVLKMLQAARDMVTTAGVSSSLDRATRTIENWGGGRRAPP 	PSPCPTPRSGPSPCLPTPDRPPEPSPTGWGPPDGGRAALVRRAPQPPGRP	PTPGPPLSDVSRVSRRPAWEARWPVRTGHCGRHLSASERPLSPARCHYSS		HASLPSSVAEAFARPSSLPAGCTGPACARPDGHSACRRLAQAQSMCLPIY
501	551 932	601	651	701

FIG. 36 (CONT.²)

1233

LESEV

1229

1228 800 850 REACQEGEQAGAPAWQHRQHVCLHAHAHLPFCWGAVCPHLPPCASHGSWL REACQEGEQAGAPAWQHRQHVCLHAHAHLPFCWGAVCPHLPPCASHGSWL SGAWGPLGHRGRTLGLGTGYRDSGGLDEISRVARGTQGFPGPCTWRRISS SGAWGPLGHRGRTLGLGTGYRDSGGLDEISXVARGTQGFPGPCTWRRISS LESEV 851 751 1129 801

FIG. 36 (CONT.³)

1 MRLAVGALLVCAVLGLCLAVPDKTVRWCAVSEHEATKCQSFRDHMKSV1F 50
51 SDGPSVACVKKASYLDCIRAIAANEADAVTLDAGLVYDAYLAPNNLKPVV 100
101 AEFYGSKEDPQTFYYAVAVVKKDSGFQMNQLRGKKSCHTGLGRSAGWNIP 150
151 IGLLYCDLPEPRKPLEKAVANFFSGSCAPCADGTDFPQLCQLCPGCGCST 200
201 LNQYFGYSGAFKCLKDGAGDVAFVKHSTIFENLANKADRDQYELLCLDNT 250
201 INQYFGYSGAFKCLKDGAGDVAFVKHSTIFENLANKADRDQYELLCLDNT 250

251	RKPVDEYKD
251	_
301	FOLFSSPHG
301	FOLFSSPHGKDLLFKDSAHGFLKVPPRMDAKMYLGYEYVTAIRNLREGTC 350
351	PEAPTDECKPVKWCALSHHERLKCDEWSVNSVGKIECVSAETTEDCIAKI 400
351	PEAPTDECK
401	MNGEADAMSLDGGEVYIAGKCGLVPVLAENYNKSDNCEDTPEAGYFAVAV 450
401	MNGEADAMSLDGGFVYIAGKCGLVPVLAENYNKSDNCEDTPEAGYFAVAV 450
451	VKKSASDLTWDNLKGKKSCHTAFGRTAGWNIPMGLLYNKINHCRFDEFFS 500
451	

FIG. 37 (CONT.¹)

501	EGCAPGSKKDSSLCKLCMGSGLNLCEPNNKEGYYGYTGAFRCLVEKGDVA	550
501		550
551	FVKHQTVPQNTGGKNPDPWAKNLNEKDYELLCLDGTRKPVEEYANCHLAR	009
551	FVKHQTVPQNTGGKNPDPWAKNLNEKDYELLCLDGTRKPVEEYANCHLAR	009
601	APNHAVVTRKDKEACVHKILRQQQHLFGSNVTDCSGNFCLFRSETKDLLF	650
601		650
651	RDDTHH.EACTFRRP	665
651		869

FIG. 37 (CONT.²)

	1 MRLAVGALLVCAVLGLCLAVPDKTVRWCAVSEHEATKCQSFRDHMKSVIP 50
51 S	
51 S	
101 7	\circ
101 7	
151	IGLLYCDLPEPRKPLEKAVANFFSGSCAPCADGTDFPQLCQLCPGCGCST 200
151	
7 102	INOYFGYSGAFKCI,KDGAGDVAFVKHSTIFRNI,ANKADRDOYFI,I,CI,DNT 250
201 I	LNQYFGYSGAFKCLKDGAGDVAFVKHSTIFENLANKADRDQYELLCLDNT 250

FIG. 38 (CONT.¹)

251	RKPVDEYKDCHLAQVPSHTVVARSMGGKEDLIWELLNQAQEHFGKDKSKE 300	0
251	RKPVDEYKDCHLAQVPSHTVVARSMGGKEDLIWELLNQAQEHFGKDKSKE 300	0
301	FOLFSSPHGKDLLFKDSAHGFLKVPPRMDAKMYLGYEYVTAIRNLREGTC 350	0
301	FQLESSPHGKDLLFKDSAHGFLKVPPRMDAKMYLGYEYVTAIRNLREGTC 350	0
351	PEAPTDECKPVKWGALSHHERLKCDEWSVNSVGKIECVSAETTEDCIAKI 400	0
351	PEAPTDECKPVKWCALSHHERLKCDEWSVNSVGKIECVSAETTEDCIAKI 400	0
401		_
401		0
448	· · · · · · · · · · · · · · · · · · ·	∞
451	VKKSASDLTWDNLKGKKSCHTAVGRTAGWNIPMGLLYNKINHCRFDEFFS 500	0

449	EGCAPGSKK
501	
499	FVKHQTVPQNTGGKNPDPWAKNLNEKDYELLCLDGTRKPVEEYANCHLAR 548
551	FVKHQTVPQNTGGKNPDPWAKNLNEKDYELLCLDGTRKPVEEYANCHLAR 600
U	
0.4.y	249 AFNHAVVIRKDKEACVHKILRQQQHLFGSNVTDCSGNFCLFRSETKDLLF 598
601	
υ υ	599 KDDTVCLAKLHDRNTYEKYLGEEYVKAVGNLRKCSTSSLLEACTFRRP 646
7 11	
TCO	KUDIVCLAKLHDKNIYEKYLGEEYVKAVGNIRKCSTSSLLEACTFRRP 698

FIG. 38 (CONT.²)

1 MAEGGEGEDEIQFLRTEDEVVLQCIATIHKEQRKFCLAAEGLGNRLCFL 50		101 RTLLYGHAVLLRHSFSGMYLTCLTTSRSQTDKLAFDVGLREHATGEACWW 	151 TIHPASKQRSEGEKVRIGDDLILVSVSSERYLHLSVSNGNIQVDASFMQT 200 	201 LWNVHPTCSGSSIEEGYLLGGHVVRLFHGHDECLTIPSTDQNDSQHRRIF 250
--	--	--	--	--

FIG. 39

251	d' .	300
251		300
301	_	350
301	OGLILQDRAKSDTKSTAFSFRASKELKEKLDSSHKRDIEGMGVPEIKYGD	350
351	SVCFVQHIASGLWVTYKAQDAKTSRLGPLKRKVILHQEGHMDDGLTLQRC	400
351	- O	400
401	OREESQAARIIRNTTALFSQFVSGNNRTAAPITLPIEEVLQTLQDLIAYF	450
401	IIRNTTALFSQFVSGNNRTAAPITLPIEEVLQTLQDLIAYF	450
451	OPPEEEMRHEDKONKLRSLKNRONLFKEEGMLALVLNCIDRLNXYNSVAH	200
451	DKONKLRSLKNRONLFKEEGMLALVLNCIDRLNVYNSVAH	500

FIG. 39 (CONT.¹)

0	DDLYSYGFDGLHLWSGRIPRAVASINQHLLRSDDVGKLLPGPRG 750	701 GGNGVGDDLYSYG	
ത	/Ul GGNGVGDDLYSYGFDGLHLWSGRIPRAVASXNQHLLRSDDVVSCCL.DLG 749 	OI GGNGVGDDLYSYG	
0	AEGSAQYKKWYFELIIDQVDPFLTAEPTHLRVGWASSSGYAPYPGGGEGW 700	651 AEGSAQYKKWYFE	
700	EGW	651 AEGSAQYKKW	
, 0	CNGVAVRANQNLICDNLLPRRNLLLQTRLINDVTSIRPNIFLGV 650	601 LCSLCLCNGVAVR	
0	LCSLCLCNGVAVRANQNLICDNLLPRRNLLLQTRLINDVTSIRPNIFLGV 650	601 LCSLCLCNGVAVR	
0		551 RLESSSGILEVLH	
0	GILEVLHCILTESPEALNLIAEGHIKSIISLLDKHGRNHKVLDI 600		
0	FAGIAREESGMAWKEILNLLYKLLAALIRGNRNNCAQFSNNLDWLISKLD 550	501 FAGIAREESGMAW	
0	EESGMAWKEILNLLYKLLAALIRGNRNNCAQFSNNLDWLISKLD 550	501 FAGIAREESGMAW	

FIG. 39 (CONT.²)

GEFR 800 QASF 849	 QASF 850 DDNK 899	 DDNK 900 EDI,K 949		KDRI 999	DRI 1000
FLPPSGYAPCYEALLPKEKMRLEPVŘEYKRDADGIRDLLGTTQFLSQASF	FLPPSGYAPCYEALLPKEKMRLEPVKEYKRDADGIRDLLGTTQFLSQASF . IPCPVDTSQVILPPHLEKIRDRLAENIHELWGMNKIELGWTFGKIRDDNK	IPCPVDTSQVILPPHLEKIRDRLAENIHELWGMNKIELGWTFGKIRDDNK IPCPVDTSQVILPPHLEKIRDRLAENIHELWGMNKIELGWTFGKIRDDNK . RQHPCLVEFSKLPETEKNYNLQMSTETLKTLLXLGCHIAHVNPAAEEDI,K		KVKLPKNYMMSNGYKPAPLDLSDVKLLPPQEILVDKLAENAHNVWAKDRI	951 KVKLPKNYMMSNGYKPAPLDLSDVKLLPPQEILVDKLAENAHNVWAKDRI
800	801	851		950	95I F

FIG. 39 (CONT.³)

1000	KOGWTYGIQQDLKNKRNPRLVPYALLDERTKKSNRDSLREAVRTFVGYGY	1049
1001		1050
1050	NIEPSDQELA	1099
1051		1100
1100	RVGWARPGCRPDVELGADDQAFVFEGNRGQRWHQGSGYFGRTWQPGDVVG	1149
1101		1150
1150	CMINLDDASMIFTLNGELLITNKGSFI,AFADYFIFNGFVPICCI,GI,SOIG	1199
1151	CMINLDDASMIFTLNGELLITNKGSELAFADYEIENGFVPICCLGLSOIG	1200
1200	RMNLGTDASTEKFYTMCGLOEGFEPFAVNMNRDVAMWFSKRLPTFVNVPK	1249
1201		1 С 1 С 1 С
- / / /		

FIG. 39 (CONT.4)

1250	DGTMDSPPCLKVTHKTFGTQNSNADMIYCRLSMPVECHSS	1299
1251		1300
1300		1349
1301	FSHSPCLDSEAFQKRKQMQEILSHTTTQCYYAIRIFGGQDPSCVWVGWVT	1350
1350	DLNKNCTVTVTLGDERGRVHESVKRSNCYMVWGGDIVASS	1399
1351	PDYHLYSEKFDLNKNCTVTVTLGDERGRVHESVKRSNCYMVWGGDIVASS	1400
1400	ORSNRSNVDLEIGCLVDLAMGMLSFSANGKELGTCYQVEPNTKVFPAVFL	1449
1401	QRSNRSNVDLEIGCLVDLAMGMLSFSANGKELGTCYQVEPNTKVFPAVFL	1450
1450	OPTSTSLFQFELGKLKNAMPLSAAIFRSEEXNPVPQCPPRLDVQTIQPVL	1499
1451	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	1500

FIG. 39 (CONT.⁵)

1500		1549
1501		1550
1550	EQEDLMRFHYHTLRLYSAVCALGNSRVAYALCSHVDLSQLFYAIDNKYLP	1599
1551	EQEDLMRFHYHTLRLYSAVCALGNSRVAYALCSHVDLSQLFYAIDNKYLP 1	1600
1600	GLLRSGFYDLLISIHLASAKERKLMMKNEYIIPITSTTRNICLFPDESKR	1649
1601	GLLRSGFYDLLISIHLASAKERKLMMKNEYIIPITSTTRNICLFPDESKR	1650
1650	HGLPGVGLRTCLKPGFRFSTPCFVVTGEDHQKQSPEIPLESLRTKALSML	1699
1651	CLKPGFRFSTPCFVVTGEDHQKQSPEIPLESLRTKALSML	1700

FIG. 39 (CONT.⁶)

1701 TEAVQCSGAHIRDPVGGSVEFQFVPVLKLIGTLLVMGVFDDDDVRQILLL 1750 IDPSVFGEHSAGTEEGAEKEEVTQVEEKAVEAGEKAGKEAPVKGLLQTRL 1751 IDPSVFGEHSAGTEEGAEKEEVTQVEEKAVEAGEKAGKEAPVKGLLQTRL 1751 IDPSVFGEHSAGTEEGAEKEEVTQVEEKAVEAGEKAGKEAPVKGLLQTRL	VLKLIGTLLVMGVFDDDDVRQILLL 1750 EEKAVEAGEKAGKEAPVKGLLQTRL 1799
IDPSVFGEHS	, , <u>,</u>
IDPSVFGEHS	, <u>,</u>
1800 PESVKLOMCELLSYLCDCELOHRVEAIVAFGDIYVSKLOANOKFRYNELM	
1801 PESVKLOMCELLSYLCDCELOHRVEAIVAFGDIYVSKLOANOKFRYNELM	AIVAFGDIYVSKLQANQKFRYNELM 18
1850 OALNMSAALTARKTKEFRSPPQEQINMLLNFQLGENCPCPEEIREELYDF	NMLLNFQLGENCPCPEEIREELYDF 189
OALNMSAALT	
1900 HEDLLIHCGVPLEEEEEEEEDTSWTGKLCALVYKIKGPPKPEKEQPTEEE	SKLCALVYKIKGPPKPEKEQPTEEE 194
HEDLLLHCGV	

FIG. 39 (CONT.7)

FIG. 39 (CONT.8)

1950	ERCPTTLKELISQTMICWAQEDQIQDSELVRMMFNLLRRQYDSIGELLQA	1999
1951		2000
2000		2049
2001	LRKTYTISHTSVSDTINLLAALGQIRSLLSVRMGKEEELLMINGLGDIMN	2050
2050		2099
(0100
2051	NKVFTQHFNLMKVLGMHETVMEVMVNVLG1ERSQ1AFFNGVASCORFLC1	0017
2100		2149
2101	FCRISRQNQKAMFEHLSYLLENSSVGLASPSMRGSTPLDVAASSVMDNNE	2150
2150	LALSLEEPDI	2199
2151		2200

2200	RFAVFVNSESVEENASVVVKLLIRRPECFGPALRGEGGNGLLAAMQGAIK	2249
2201	RFAVEVNSESVEENASVVVKLLIRRPECFGPALRGEGGNGLLAAMQGAIK	2250
2250	ISENPALDLPSQGYKREVSTEDDEEEEEIVHMGNAIMSFYSALIDLLGRC	2299
2251	ISENPALDLPSQGYKREVSTEDDEEEEEIVHMGNAIMSFYSALIDLLGRC	2300
2300	APEMHLIQTGKGEAIRIRSILRSLVPTEDLVGIISIPLKLPSLNKDGSVS	2349
2301	APEMHLIQTGKGEAIRIRSILRSLVPTEDLVGIISIPLKLPSLNKDGSVS	2350
2350	EPDMAXNECPDHKAPMVLFLDRVYGIKDQTFLLHLLEVGFLPDLRASASL	2399
2351	EPDMAGNECPDHKAPMVLFLDRVYGIKDQTFLLHLLEVGFLPDLRASASL	2400
2400	DTVSLSTTEAALALNRYICSAVLPLLTRCAPLFXGTEHCTSLIDSTLQTI	2449
2401	DTVSLSTTEAALALNRYICSAVLPLLTRCAPLFGGTEHCTSLIDSTLQTI	2450

FIG. 39 (CONT.⁹)

FIG. 39 (CONT. 10)

FIG. 39 (CONT. 11)

2700	ENEKLRSVSQANQGNSYSPAPLDLSNVVLSRELQGMVEVVAENYHNIWAK	2749
2701	ENEKLRSVSQANQGNSYSPAPLDLSNVVLSRELQGMVEVVAENYHNIWAK	2750
2750	KKKLELESKGGGSHPLLVPYDTLTAKEKFKDREKAQDLFKFLQVNGIIVS	2799
2751		2800
7800	2800 RGMKDMELDASSMEKRFXYKFLKKILKYVDSAQEFIAHLEAIVSSGKTEK	2849
) (2850
7807		(
2850	SPRDQEIKFF	ת ת ת
2851		2900
 		5
2900	_	7343
		り の に り
2901	VAGLECKLAALVRHRISLFGSDSTTMVSCLHILAQTLDIKIVMRSGSELV	000

FIG. 39 (CONT. 12)

٠					_	_	_	
2999	3049	3050	3099	3100	3149	3150	3199	3200
2950 KAGLRAFFENAAEDLEKTSENLKLGKFTHSRTQIKGVSQNINYTTVALLP	ILTSIFEHVTQHQFGMDLLLGDVQISCYHILCSLYSLGTGKNIYVERQRP	3001 ILTSIFEHVTQHQFGMDLLLGDVQISCYHILCSLYSLGTGKNIYVERQRP	3050 ALGECLASLAAAIPVAFLEPTLNRYNPLSVFNTKTPRERSILGMPDTVED	3051 ALGECLASLAAAIPVAFLEPTLNRYNPLSVFNTKTPRERSILGMPDTVED	3100 MCPDIPQLEGLMKEINDLAESGARYTEMPHVIEVILPMLCNYLSYWWERG	3101 MCPDIPQLEGLMKEINDLAESGARYTEMPHVIEVILPMLCNYLSYWWERG	3150 PENLPPSTGPCCTKVTSEHLSLILGNILKIINNNLGIDEASWMKRIAVYA	3151 PENLPPSTGPCCTKVTSEHLSLILGNILKIINNNLGIDEASWMKRIAVYA

3200	•	3249
3201	OPIISKARPDLLRSHFIPTLEKLKKKAVKTVQEEEQLKADGKGDTQEAEL	3250
3250		3299
3251		3300
3300	ILWCKSHNFK	3349
3301		3350
3350	RRGDLYSIQT	3399
3351		3400
3400		3449
3401		3450

FIG. 39 (CONT. 13)

3450	SAAVFHLEQVEQPLRSKKAVWHKLLSKQRKRAVVACFRMAPLYNLPRHRS	3499
3451	SAAVFHLEQVEQPLRSKKAVWHKLLSKQRKRAVVACFRMAPLYNLPRHRS	3500
3500	. INLFLHGYQRFWIETEEYSFEEKLVQDLAKSPKVEEEEEEETEKQPDPLH	3549
3501	INLFLHGYQRFWIETEEYSFEEKLVQDLAKSPKVEEEEEEETEKQPDPLH INLFLHGYQRFWIETEEYSFEEKLVQDLAKSPKVEEEEEETEKQPDPLH	3550
3550	OIILYFSRNALTERSKLEDDPLYTSYSSMMAKSCOSGEDEEEDEDKEKTF	3599
3551	QIILYFSRNALTERSKLEDDPLYTSYSSMMAKSCQSGEDEEEDEDKEKTF	3600
3600	EEKEMEKOKTLYQQARLHERGAAEMVLQMISASKGEMSPMVVETLKLGIA	3649
3601	EEKEMEKQKTLYQQARLHERGAAEMVLQMISASKGEMSPMVVETLKLGIA	3650
3650	ILNGGNAGVQQKMLDYLKEKKDAGFFQSLXGLMQSCSVLDLNAXERQNKA	3699
3651	ILNGGNAGVQQKMLDYLKEKKDAGFFQSLPGLMQSCSVLDLNASERQNKA	3700

FIG. 39 (CONT: 14)

FIG. 39 (CONT. 15)

3700		3749
3701	EGLGMVTEEGTLIVRERGEKVLQNDEFTRDLFRFLQLLCEGHNSDFQNFL	3750
3750	RTQMGNTTTVNVIISTVDYLLRLQESISDFYWYYSGKDIIDESGQHNFSK	3799
3751		3800
3800	ALAVTKQI FNSLTEYIQGPCI GNQOSLAHSRLWDAVVGFLHVFANMQMKL	3849
3801	•	3850
3850	SQDSSQIELL	3899
3851	SQDSSQIELLKELLDLLQDMVVMLLSLLEGNVVNGTIGKQMVDTLVESST	3900
3900		3949
3901	NVEMILKFFDMFLKLKDLTSSDTFKEYDPDGKGIISKKEFQKAMEGQKQY	3950

FIG. 39 (CONT. 16)

3950	-	3999
3951	1008EIDFLLSCAEADENDMFNYVDFVDRFHEPAKDIGFNVAVLLTNLSEH	4000
4000	MPNDSRIKTINYEZEMTATAS IVOXAVNIVSAROGIITOMISRIKATANIVA	0 / 0 /
) () (
4 0 0 I	MPNDSKLKCLLDPAESVLNYFGPYLGRIEIMGGAKKIERVYFEISESSRT	4050
4050		4099
t (,
4051	QWEKPQVKESKRQFIFDVVNEGGEQEKMGLFVNFCEDTIFEMQLASQISE	4100
4100	SDSADRPEEEEDEDSSYVLEIAGEEEEDGSLEPASAFAMACASVKRNVT	4149
4101	SDSADRPEEEEEDEDSSYVLEIAGEEEEDGSLEPASAFAMACASVKRNVT	4150
4150	DFLKRATLKNLRKQYRNVKKMTAKELVKVLFSFFWMLFVGLFQLLFTILG	4199
4151	DFLKRATLKNLRKQYRNVKKMTAKELVKVLFSFFWMLFVGLFQLLFTILG	4200

	4.450	YLARNFYNLRFLALFVAFAINFILLFYKVTEEPLEEETEDVANLWNSFND	4401
~	4449	YLARNFYNLRFLALFVAFAINFILLFYKVTEEPLEEETEDVANLWNSFND	4400
	4400	KDKEEEQAEYLWTEVTKKKKRRCGQKVEKPEAFTANFFKGLEIYQTKLLH	4351
~	4399	KDKEEEQAEY	4350
	4350		4301
0	4349	EIIGKDEPPTLESTVQKKRKAQAAEMKAANEAEGKVESEKADMEDGEKED	4300
	4300		4251
\bigcirc	4299	VMEPGITTELVHFIKGEKGDTDIMSDLFGLHPKKEGSLKHGPEVGLGDLS	4250
0	425(4201
\mathcal{L}	424	4200 GIFQILWSTVFGGGLVEGAKNIRVTKILGDMPDPTQFGIHDDTMEAERAE 4249	4200

FIG. 39 (CONT.¹⁷)

4700	L TLRTILSSVTHNGKQLVLTVGLLAVVVYLYTVVAFNFFRKFYNKSEDDDE	4651
)) !"
0	TOOLS NIVER CONTRACT TO THE TOTAL TO TO THE TERM TO THE THE TERM TO THE THE TERM TO THE TE	L
4650		4601
4649		4600
4600		4551
4599	بكر	4550
4550		4501
4549		4500
4500	EEEEEEAMVFFVLQESTGYMAPTLRALAIIHTIISLVCVVGYYCLKVPLVV	4451
4499		4450

FIG. 39 (CONT. 18)

4750 4749 PDMKCDDMMTCYLFHMYVGVRAGGGIGDEIEDPAGDPYEMYRIVFDITFF PDMKCDDMMTCYLFHMYVGVRAGGGIGDEIEDPAGDPYEMYRIVFDITFF 4783 4784 FFVIVILLAIIQGLIIDAFGELRDQQEQVREDME FFVIVILLAIIQGLIIDAFGELRDQQEQVREDME 4750 4751

4700

4701

FIG. 39 (CONT. 19)

250	201 GCKI,SI,VFI,OYCIMANFFWLL,VEGLYLHTLLVAMLPPRRCFLAYLLIGWG	
250	201 GCKLSLVFLQYCIMANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWG	
200	151 FRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQPSSWV	
200	151 FRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQPSSWV	
150	101 TFPDFVDACGYSDPEDESKITFYILVKAIYTLGYSVSLMSLATGSIILCL	
150	101 TFPDFVDACGYSDPEDESKITFYILVKAIYTLGYSVSLMSLATGSIILCL	
100		
100	51 ACSGVWDNITCWRPANVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSE	
50		
50	1 MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCXELLRSQTEKHK	

FIG. 4(

251	LPTVCIGAWTAARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFI	300
251	LPTVCIGAWTAARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFI	300
301	SIIRILLQKLTSPDVGGNDQSQYKRLAKSTLLLIPLFGVHYMVFAVFPIS	350
301	SIIRILLQKLTSPDVGGNDQSQYKRLAKSTLLLIPLFGVHYMVFAVFPIS	350
	•	
·	351 ISSKYQILFELCLGSFQ 367	
	351 ISSKYQILFELCLGSFQ 367	,

FIG. 40 (Cont. 1)

1 MAGVVHVSLAALLLLPMAPAMHSDCIFKKEQAMCLEKIQKANELMGFNDS 30
51 SPGCPGMWDNITCWKPAHVGEMVLVSCPELFRIFNPDQ 88
C1 COCOCOMMITTION FOR TAXACOBILE BY TENDOCYMETET GESOF 100
89DMGVVSRNCTEDGWSEPFPHYFDACGFDEYESETGDQDYYY 129
101 GDSNSLDLSDMGVVSRNCTEDGWSEPFPHYFDACGFDEYESETGDQDYYY 150
130 LSVKALYTVGYSTSLVTLTTAMVILCRFRKLHCTRNFIHMNLFVSFMLRA 179
151 LSVKALYTVGYSTSLVTLTTAMVILCRFRKLHCTRNFIHMNLFVSFMLRA 200
180 ISVFIKDWILYAEQDSNHCFISTVECKAVMVFFHYCVVSNYFWLFIEGLY 229
201 ISVFIKDWILYAEQDSNHCFISTVECKAVMVFFHYCVVSNYFWLFIEGLY 250

FIG. 41

230 LFTLLVETFFPERRYFYWYTIIGWGTPTVCVTVWATLRLYFDDTGCWDMN		279
251 LFTLLVETFFPERRYFYWYTIIGWGTPTVCVTVWATLRLYFDDTGCWDMN		300
280 DSTALWWVIKGPVVGSIMVNFVLFIGIIVILVQKLQSPDMGGNESSIYLR		329
301 DSTALWWVIKGPVVGSIMVNFVLFIGIIVILVQKLQSPDMGGNESSIYLR	\sim	250
330 LARSTLLIPLEGIHYTVFAFSPENVSKRERLVFELGLGSFQGFVVAVLY		379
351 LARSTLLIPLFGIHYTVFAFSPENVSKRERLVFELGLGSFQGFVVAVLY		400
380 CFLNGEVQAEIKRKWRSWKVNRYFAVDFKHRHPSLASSGVNGGTQLSILS		429
401 CFLNGEVQAEIKRKWRSWKVNRYFAVDFKHRHPSLASSGVNGGTQLSILS	4	50
430 KSSSQIRMSGLPADNLAT 447		
451 KSSSQIRMSGLPADNLAT 468		

FIG. 41 (CONT. 1)

FIG. 42 (CONT.¹)

7	1 MERGLPLLCAVLALVLAPAGAFRNDECGDTIKIESPGYLTSPGYPHSYHP	50
51	SEKCEWLIQAE	100
51	SEKCEWLIQAPDPYQRIMINFNPHFDLEDRDCKYDYVEVFDGENENGHFR	100
101	GKECGKIAPP	150
101	GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN	150
151	•	200
151	YTTPSGVIKSPGFPEKYPNSLECTYIVFAPKMSEIILEFESFDLEPDSNP	200
201	PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD	250
201		250

FIG. 43

FIG. 43 (CONT.

	
ਜ	MGRVGYWTLLVLPALLVWRGPAPSAAAEKGPPALNIAVMLGHSHDVTERE 50
51	LRTLWGPEQAAGLPLDVNVVALLMNRTDPKSLITHVCDLMSGARIHGLVF 100
51	LRTLWGPEQAAGLPLDVNVVALLMNRTDPKSLITHVCDLMSGARIHGLVF 100
101	_
•	
101	GDDTDQEAVAQMLDF1SSH1FVF1LG1HGGASM1MADADF1S1FFQFGAS
151	
151	IQQQATVMLKIMQDYDWHVFSLVTTIFPGYREFISFVKTTVDNSFVGWDM 200
201	ONVITEDTSFEDAKTOVOLKKIHSSVILLYCSKDEAVLILSEARSLGLTG 250
 	
201	ONVITT DTSFEDAKTOVOLKKIHSSVILLYCSKDEAVLILSEARSLGLTG 250

FIG. 44

251	YDFFWIVPSLVSGNTELIPKEFPSGLISVSYDDWDYSLEARVRDGIGILT	300
251	YDFFWIVPSLVSGNTELIPKEFPSGLISVSYDDWDYSLEARVRDGIGILT	300
301	TAASSMLEKFSYIPEAKASCŶGQMERPEVPMHTLHPFMVNVTWDGKDLSF	350
301	TAASSMLEKFSYIPEAKASCYGQMERPEVPMHTLHPFMVNVTWDGKDLSF	350
351	TEEGYQVHPRLVVIVLNKDREWEKVGKWENHTLSLRHAVWPRYKSFSDCE	400
ר 1		400
1))
401	PDDNHLSIVTLEEAPFVIVEDIDPLTETCVRNTVPCRKFVKINNSTNEGM	450
401	PDDNHLSIVTLEEAPFVIVEDIDPLTETCVRNTVPCRKFVKINNSTNEGM	450
 	•	
451	NVKKCCKGFCIDILKKLSRTVKFTYDLYLVTNGKHGKKVNNVWNGMIGEV	200
451	NVKKCCKGFCIDILKKLSRTVKFTYDLYLVTNGKHGKKVNNVWNGMIGEV	200

FIG. 44 (CONT. 1)

501	501 VYQRAVMAVGSLTINEERSEVVDFSVPFVETGISVMVSRSNGTVSPSAFL 550	
501	VYQRAVMAVGSLTINEERSEVVDFSVPFVETGISVMVSRSNGTVSPSAFL 550	
551	EPFSASVWVMMFVMLLIVSAJAVFVFEYFSPVGYNRNLAKGKAPHGPSFT 600	
551	EPFSASVWVMMFVMLLIVSAIAVFVFEYFSPVGYNRNLAKGKAPHGPSFT 600	
601	IGKAIWLLW	
601		
651	AFMIOEEFV	
1		
651	_	

FIG. 44 (CONT.²)

701	7	
701	HILLILILILILILILILILILILILILILILILILILI	
751	GSGYIFATTGYGIALQKGSPWKRQIDLALLQFVGDGEMEELETLWLTGIC 800	
751	GSGYIFATTGYGIALQKGSPWKRQIDLALLQFVGDGEMEELETLWLTGIC 800	
1		
801	C	
801	HNEKNEVMSSQLDIDNMAGVFYMLAAAMALSLITFIWEHLFYWKLKFCFI	
851	GVCSDRFGLLFSTSKGITSCINGVILLERMANSSTSTSTSTSTSTSTSTSTSTSTSTSTSTSTSTSTSTS	
851	GVCSDRPGL	
	040 OHBANUSAMINOMETERSON.	
901	AKNISSMSNMNSSRMDSPKRAADFIQRGSLIMDHVSDNGNEHISDNING S	
	050 OHSHILLING THE THE TOTAL TWO WINDERS TO BE SEED BY SECTION OF THE SECTION OF	
901)	

FIG. 44 (CONT.³)

951	GKESIFGDNMNELQTFVANRQKDNLNNYVFQGQHPLTLNESNPNTVEVAV 1000
951	GKESIFGDNMNELQTFVANRQKDNLNNYVFQGQHPLTLNESNPNTVEVAV 1000
1001	STESKANSRP
1001	STESKANSRPRQLWKKSVDSIRQDSLSQNPVSQRDEATAENRTHSLKSPR 1050
1051	YLPEEMAHSD
1051	
1101	
1101	
1151	YQDPSENFRKGDSTLPMNRNPLHNEEGLSNNDQYKLYSKHFTLKDKGSPH 1200
1151	

FIG. 44 (CONT. 4)

FIG. 44 (CONT.⁵)

1201	STHCRSCLSNMPTYSGHFTMRSPFKCDACLRMGNLYDIDE	1250
1201		1250
		{ •
1251		1257
		(
1251	DOMLQETGNPATGEQVYQQDWAQNNALQLQKNKLRISRQHSYDNIVDKPR	1300
	•	
1258	RDDQRLVIGRCPSDPYKHSLPSQAVNDSY	1286
1351	SKRSKSLLPDHTSDNPFLHSHR	1400
		•
1287	LRSSLRSTAS	1336
		1
1401		1450
	•	
	1337 RRVYKKMPSIESDV.1350	
•	1451 RRVYKKMPSIESDV 1464	

1 MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCXELLRSQTEKHK	SIHPECRFHLEIQEEETKCXELLRSQTEKHK 50
51 ACSGVWDNITCWRPANVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSE	FVTVPCPKVFSNFYSKAGNISKNCTSDGWSE 100
51 ACSGVWDNITCWRPANVGETVTVPCPKVFSNF	TCWRPANVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSE 100
101 TFPDFVDACGYSDPEDESKITFYILVKAIYT	TFPDFVDACGYSDPEDESKITFYILVKAIYTLGYSVSLMSLATGSIILCL 150
101 TFPDFVDACGYSDPEDESKITFYILVKAIYT	
MANY 1470 TAG ITAG ITA INTITAMBELLA 144 P. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	
TOT FREEHCTRNITHENETERSTEEL TOTAL OF THE LITTLE TO THE LIT	
151 FRKLHCTRNYIHLNLFLSFILRAISVLVKDD	FRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQPSSWV 200
201 GCKLSLVFLQYCIMANFFWLLVEGLYLHTLL	GCKLSLVFLQYCIMANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWG 250
201 GCKLSLVFLQYCIMANFFWLLVEGLYLHTLL	GCKLSLVFLQYCIMANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWG 250

251	LPTVCIGAW	300	
251	LPTVCIGAWTAARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFI	300	
301	SIIRILLQKLTSPDVGGNDQSQYKRLAKSTLLLIPLFGUHYMVFAVFPIS	350	
301	SIIRILLOK	350	
	351 ISSKYQILFELCLGSFQGLVVAVLYCFLNSEV 382		
	351 TSSKYOTIFFICIGSFOGLWANIYCFINSFW 382		

FIG. 45 (CONT.¹)

250	201 GCKLSLVFLQYCIMANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWG	
250	GCKLSLVF	
200		
200	151 FRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQPSSWV	
150	101 TFPDFVDACGYSDPEDESKITFYILVKAIYTLGYSVSLMSLATGSIILCL	
150		
100	51 ACSGVWDNITCWRPANVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSE	
100	51 ACSGVWDNITCWRPANVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSE	
50		
20	1 MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCXELLRSQTEKHK	

FIG. 4(

		351 ISSKYQILFELCLGSFQGLVVAVLYCFLNSEV 382 	
	350		
	350	301 SIIRILLQKLTSPDVGGNDQSQYKRLAKSTLLLIPLFGVHYMVFAVFPIS	
	300	251 LPTVCIGAWTAARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFI	
_	300	AARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFI	

FIG. 46 (CONT.¹)

-	MKSGSGGGSPTSLWGLLFLSAALSLWPTSGEICGPGIDIRNDYQQLKRLE 50
<u>Н</u>	MKSGSGGGSPTSLWGLLFLSAALSLWPTSGEICGPGIDIRNDYQQLKRLE 50
51	NCTVIEGYLHILLISKAEDYRSYRFPKLTVITEYLLLFRVAGLESLGDLF 100
51	NCTVIEGYLHILLISKAEDYRSYRFPKLTVITEYLLIFRVAGLESLGDLF 100
101	PNLTVIRGWKLFYNYALVIFEMTNLKDIGLYNLRNITRGAIRIEKNADLC 150
101	PNLTVIRGWKLFYNYALVIFEMTNLKDIGLYNLRNITRGAIR1EKNADLC 150
151	YLSTVDWSLILDAVSNNYIVGNKPPKECGDLCPGTMEEKPMCEKTTINNE 200
151	YLSTVDWSLILDAVSNNYIVGNKPPKECGDLCPGTMEEKPMCEKTTINNE 200
201	YNYRCWTTNRCQKMCPSTCGKRACTENNECCHPECLGSCSAPDNDTACVA 250
201	YNYRCWTTNRCQKMCPSTCGKRACTENNECCHPECLGSCSAPDNDTACVA 250

FIG. 47 (CONT. 1)

. v	251	CRHYYYAGVCVPACPPNTYRFEGWRCVDRDFCANILSAESSDSEGFVIHD	300
• •	251		300
` '	301	GECMOECPSGFIRNGSOSMYCIPCEGPCPKVCEEEKKTKTIDSVTSAOML	350
•			1
. ,	301	GECMQECPSGFIRNGSQSMYCIPCEGPCPKVCEEEKKTKTIDSVTSAQML 3	350
` '	351	QGCTIFKGNLLINIRRGNNIASELENFMGLIEVVTGYVKIRHSHALVSLS 4	400
• •	351	QGCTIFKGNLLINIRRGNNIASELENFMGLIEVVTGYVKIRHSHALVSLS 4	400
	401	FLKNLRLILGEEQLEGNYSFYVLDNQNLQQLWDWDHRNLTIKAGKMYFAF 4	45.0
•	401	FLKNLRLILGEEQLEGNYSFYVLDNQNLQQLWDWDHRNLTIKAGKMYFAF 4	450
٦	451	NPKLCVSEIYRMEEVTGTKGRQSKGDINTRNNGERASCESDVLHFTSTTT 5	500
4	451	NPKLCVSEIYRMEEVTGTKGROSKGDINTRNNGERASCESDVLHFTSTTT	200

FIG. 47 (CONT.²)

501	SKNRIIITWHRYRPPDYRDLISFTVYYKEAPFKNVTEYDGQDACGSNSWN 550
501	SKNRIIITWHRYRPPDYRDLISFTVYYKEAPFKNVTEYDGQDACGSNSWN 550
551	MVDVDLPPN
551	
601	
. 601	
ر 1	OPODGYLYRHNYCSKDKIPIRKYADGTIDIEEVTENPKTEVCGGEKGPCC 700
)	
651	OPQDGYLYRHNYCSKUKIPIKKYADGIIDIEEVIENFAIEVOGGENGFOO
701	•
701	ACPKTEAEKQAEKEEAEYRKVFENFLHNSIFVPRPERKKRDVMQVANTTM / JU

751	
751	
Ω Ω	10 ta towaa aa ammiga oa taa koa kama kanakana kaoo taa kaanano kana kana kana kana kana kana
9	
801	IDIHSCNHE
851	KWPEPENPNGLILMYFIKYGSOVFDORFCVSROFYRKYGGAKLNRLNPGN 900
851	KWPEPENPN
•	
901	YTARIQATS
,	
901	YTARIQATSLSGNGSWTDPVFFYVQAKTGYENFIHLIIALPVAVLLIVGG 950
951	LVIMLYVFHRKRNNSRLGNGVLYASVNPEYFSAADVYVPDEWEVAREKIT 1000
951	LVIMLYVFHRKRNNSRLGNGVLYASVNPEYFSAADVYVPDEWEVAREKIT 1000

FIG. 47 (CONT.³)

1001	MSBFICOGSFCMVVFCVVKOFDFDFTRVATKTVNFAASMBFRTFNFNF	1050
H D H)))
1001		1050
1051	ASVMKE FNCHHVVRLLGVVŠQGQPTLVIMELMTRGDLKSYLRSLRPEMEN	1100
1051	ASVMKEFNCHHVVRLLGVVSQGQPTLVIMELMTRGDLKSYLRSLRPEMEN	1100
1101		1150
1101	NPVLAPPSLSKMIQMAGEIADGMAYLNANKFVHRDLAARNCMVAEDFTVK	1150
1151	IGDFGMTRDIYETDYYRKGGKGLLPVRWMSPESLKDGVFTTYSDVWSFGV	1200
1151	IGDFGMTRDIYETDYYRKGGKGLLPVRWMSPESLKDGVFTTYSDVWSFGV	1200
1201	VLWEIATLAEQPYQGLSNEQVLRFVMEGGLLDKPDNCPDMLFELMRMCWQ	1250
1201	VLWEIATLAEQPYQGLSNEQVLRFVMEGGLLDKPDNCPDMLFELMRMCWQ	1250

FIG. 47 (CONT.4)

12//	1300	1327	1350		
1/71 MNDKMRPSFTEIISSIKEELDLEPENM 12/	YNPKMRPSFLEIISSIKEEMEPGFREVSFYYSEENKLPEPEELDLEPENM	1278 ESVPLDPSASSSSLPLPDRÅSGHKAENGPGPGVLVLRASFDERQPYAHMN		1328 GGRKNERALPLPQSSTC 1344	

FIG. 47 (CONT.⁵)

()
1 MERGLPLLCAVLALVLAPAGAFRNDECGDTIKIESPGYLTSPGYPHSYHP 50
•
51 SEKCEWLIQAPDPYQRIMINFNPHFDLEDRDCKYDYVEVFDGENENGHFR 100
51 SEKCEWLIQAPDPYQRIMINFNPHFDLEDRDCKYDYVEVFDGENENGHFR 100
101 GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN 150
101 GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN 150
151 YTTPSGVIKSPGFPEKYPNSLECTYIVFAPKMSEIILEFESFDLEPDSNP 200
151 YTTPSGVIKSPGFPEKYPNSLECTYIVFAPKMSEIILEFESFDLEPDSNP 200
201 PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD 250
201 PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD 250

251	SAIAKEGFS
251	
301	WSAERSRLN
301	
351	KKYYVKTYK
351	124
401	TREVRIKPA
401	TRFVRIKPATWETGISMRFEVYGCKITDYPCSGMLGMVSGLISDSQITSS 450
451	NOGDRNWME
451	

FIG. 48 (CONT.¹)

550	550	009	009		
501 QGGKHRENKVFMRKFKIGYSNNGSDWKMIMDDSKRKAKSFEGNNNYDTPE 550	 1 QGGKHRENKVFMRKFKIGYSNNGSDWKMIMDDSKRKAKSFEGNNNYDTPE	1 LRTFPALSTRFIRIYPERATHGGLGLRMELLGCEVEAPTAGPTTPNGNLV	1 LRTFPALSTRFIRIYPERATHGGLGLRMELLGCEVEAPTAGPTTPNGNLV	601 DECDDDQANCHSGTGDDFQLTGGTTVLATEKPTVIDSTIQS 641	601 DECDDDQANCHSGTGDDFQLTGGTTVLATEKPTVIDSTIQS 641
50	501	551	551		

FIG. 48 (CONT.²)

250		
250	201 PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD	
200	151 YTTPSGVIKSPGFPEKYPNSLECTYIVFAPKMSEIILEFESFDLEPDSNP	
007	151 YTTPSGVIKSPGFPEKYPNSLECTYIVEAPKMSELLLEFESFULEFUSNP 	
	•	
150	101 GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN	
150	101 GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN	
100	51 SEKCEWLIQAPDPYQRIMINFNPHFDLEDRDCKYDYVEVFDGENENGHFR	
100		
20		
5 0		
(THE THE PARTY OF T	

251	SAIAKEGFSANYSVLQSSVSEDFKCMEALGMESGEIHSDQITASSQYSTN 300
251	
100	WAS TO BE A TOWN TOWN TOWN TOWN TOWN TOWN TOWN TOWN
7 O C	
301	WSAERSRINYPENGWTPGEDSYREWIQVDLGLLRFVTAVGTQGAISKETK 350
351	KKYYVKTYKIDVSSNGEDWITIKEGNKPVLFQGNTNPTDVVVAVFPKPLI 400
	•
351	KKYYVKTYKIDVSSNGEDWITIKEGNKPVLFQGNTNPTDVVVAVFPKFLL 400
•	ORD SOUTORUST IDSIMO IMOSOGNABIA ON STIER CONTRA CO
401)
101	THE TREATMETERS OF THE FORMULT OF TH
†	
451	NQGDRNWMPENIRLVTSRSGWALPPAPHSYINEWLQIDLGEEKIVRGI
451	NQGDRNWMPENIRLVTSRSGWALPPAPHSYINEWLQIDLGEEKIVRGIII 500

FIG. 49 (CONT.¹)

							*
538		567	650	617	700	199	750
501 QGGKHRENKVFMRKFKIGYSNNGSDWKMIMDDSKRKAK	**	539	601 DECDDDQANCHSGTGDDFQLTGGTTVLATEKPTVIDSTIQSEFPTYGFNC	568 EFGWGSHKTFCHWEHDNHVQLKWSVLTSKTGPIQDHTGDGNFIYSQADEN		618 QKGKVARLVSPVVYSQNSAHCMTFWYHMSGSHVGTLRVKLRYQKPEEYDQ	701 QKGKVARLVSPVVYSQNSAHCMTFWYHMSGSHVGTLRVKLRYQKPEEYDQ
υ <u>υ</u>		5	9	5	9	9	7

FIG. 49 (CONT.²)

	818 FELVDGVKLKKDKLNTQSTYSEA 840 	
006	851 LKTLEPILITIIAMSALGVLLGAVCGVVLYCACWHNGMSERNLSALENYN	8
817	768 LKTLXPILITIIAMSALGVLLGAVCGVVLYCACWHNGMSERNLSALENYN	76
850	801 NNHISQEDCAKPADLDKKNPEIKIDETGSTPGYEGEGEGDKNISRKPGNV	8(
767	CAKPADLDKKNPEIKIDETGSTPGYEGEGEGDKNISRKPGNV	7.1
800		75
717	668 LVWMAIGHQGDHWKEGRVLLHKSLKLYQVIFEGEIGKGNLGGIAVDDISI	99

FIG. 49 (CONT.³)

1 MERGLPLLCAVLALVLAPAGAFRNDKCGDTIKIESPGYLTSPGYPHSYHP 50
AVLALVLAPAGAFRNDECGDTIKIESPGYLTSPGYPHS
100 THE STATE OF THE TOTAL THE TOTAL
4
51 SEKCEWLIQAPDPYQRIMINFNPHFDLEDRDCKYDYVEVFDGENENGHFR 100
101 GKECGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRKELFKKGFECSON 130
101 GKFCGKIAPPPVVSSGPFLFIKFVSDYETHGAGFSIRYEIFKRGPECSQN 150
(
>
201 PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD 250
201 PGGMFCRYDRLEIWDGFPDVGPHIGRYCGQKTPGRIRSSSGILSMVFYTD 250
(
SANYSVLQSSVSEDFKCMEALGMESGEIHSDQITASSQY
; ;
251 SAIAKEGFSANYSVLQSSVSEDFKCMEALGMESGEIHSDQITASSQYSTN 300

301	WSAERSRINYPENGWTPGEDSYREWIQVDLGLLRFVTAVGTQGAISKETK	350
301	WSAERSRINYPENGWTPGEDSYREWIQVDLGLLRFVTAVGTQGAISKETK	350
351	KKYYVKTYKIDVSSNGEDWIŢIKEGNKPVLFQGNTNPTDVVVAVFPKPLI	400
351		400
401	TRFVRIKPATWETGISMRFEVYGCKITDYPCSGMLGMVSGLISDSQITSS	450
401		450
451	⊢	200
451		200
	501 QGGKHRENKVFMRKFKIGYSNNGSDWKMIMDDSKRKAR 538	

FIG. 50 (CONT.¹)

H H	MGAPACALALCVAVAIVAGASSESLGTEQRVVGRAAEVPGPEPGQQEQLV 50
51	FGSGDAVELSCPPPGGGPMGPŢVWVKDGTGLVPSERVLVGPQRLQVLNAS 100
51	
101	HEDSGAYSCRORLTORVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGA 150
101	
151	PYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREFRGEHR 200
151	
201	IGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSP 250
201	201 IGGIKLRHOOWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSP 250

SAWLVV

 $(CONT.^{1})$ 51 FIG.

1 MTLRHLPFILLILSGELYAEEKQCDFPTVENGRIAQYYYTFKSFYFPMS 50
1 MTLRHLPFILLILSGELYAEEKQCDFPTVENGRIAQYYYTFKSFYFPMS 50
•
51 VDKKLSFFCLAGYATESGKQEEQIRCTAEGWSPNPRCYKKCLKPDLRNGY 100
101 VSNDKVLYKLQERMSYGCSSGYKTTGGKDEEVVHCLSAGWSSQFSCKKEQ 100
101 VSNDKVLYKLQERMSYGCSSGYKTTGGKDEEVVHCLSAGWSSQFSCAMAF 199
EHGNYSTTORTEKVKDIVAYICIAGIIIIIGNQIGEAEOQAM
151 ETCLAPELEHGNYSTTQRTFKVKDIVAYTCTAGYYTTTGKQTGEAECQAN ZUU
201 GWSLTPQCNKLMCSSLRLIENGYFHPVKQTYEEGDVVQFFCHENYYLSGS 250
201 GWSLTPQCNKLMCSSLRLIENGYFHPVKQTYEEGDLVQFFCHENYYLSGS 250

	301 ECELNFVIQGSEELLCENGKWTEPPKCI 328
300	251 DLIQCYNFGWYPESPICEGRRNRCPPPVPLNSKIQPHSTTYRHGERVHI
300	251 DLIQCYNFGWYPESPICEGRRNRCPPPPVPLNSKIQPHSTTYRHGERVHI

FIG. 52 (CONT.¹)

	MPWGRRPTWLLLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG 50
51	PAPFLVFSQGKSISRIDPDGTNHQQLVVDAGISADMDIHYKKERLYWVDV 100
51	PAPFLVFSQGKSISRIDPDGTNHQQLVVDAGISADMDIHYKKERLYWVDV 100
101	FROVILRVFLNGTGLEKVCNVERKVSGLAIDWIDDEVLWVDQQNGVITVT 150
101	FROVLLRVFLNGTGLEKVCNVERKVSGLAIDWIDDEVLWVDQQNGVITVT 150
! !	OV NUUNE SHIRAHIROMEMEMETERIKETIKETIK TOOF TOOF TOOLOOF
151	
151	DMTGKNSRVLLSSLKHPSNIAVDPIERLMFWSSEVTGSLHRAHLKGVDVK 200
	056 OHBITAMORETAKIIDOEOGO
201	TLLETGGISVLTLDVLDKRLFWVQDSGEGSHAITHSCDIEGGSVruit 200
201	
251	ARHSLSSMAFFGDRIFYSVLKSKAIWIANKHTGKDTVRINLHPSFVTFGK 300
251	ARHSLSSMAFFGDRIFYSVLKSKAIWIANKHIGKDIVKINLHFSFVIFGK 300

FIG. 53 (CONT. 1)

	0 0	0 0	00	0 0	000	
650	700	7.5	φ φ	1 85 1 85	0 0 0	
601 ERISRPRGIAVHPRARRLFWTDVGMSPRIESASLQGSDRVLIASSNLLEP 	51	01	751 CLYRNGGCEHICQESLGTARCLCREGFVKAWDGKMCLPQDYPILSGENAD 	801 LSKEVTSLSNSTQAEVPDDDGTESSTLVAEIMVSGMNYEDDCGPGGCGSH 	851 ARCVSDGETAECQCLKGFARDGNLCSDIDECVLARSDCPSTSSRCINTEG	FIG. 53 (CONT. ²)

53 (Cont.³)

Fig.

851		00
851	ARCVSDGETAECQCLKGFARDGNLCSDIDECVLARSDCPSTSSRCINTEG	006
901	GYVCRCSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR	950
901	GYVCRCSEGYEGDGISCFDIDECQRGAHNCAENAACTNTEGGYNCTCAGR	950
951	PSSPGLSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE	1000
951	PSSPGRSCPDSTAPSLLGEDGHHLDRNSYPGCPSSYDGYCLNGGVCMHIE 10	1000
1001	SLDSYTCNCVIGYSGDRCQT	1020
1001		1050
1021		1056
1151	PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG	1200
	1057 SCHERAPDLPRQTEPVQ 1073	

FIG. 54 (CONT. 1)

300	300	50	C	330	400	(400	150		450	1	500	· (
ARHSLSSMAFFGDRIFYSVLKSKAIWIANKHTGKDTVRINLHPSFVTPGK		AKHOLOGICI INTERPORTATION OF THE SACAES 3	LMVVHPRAQPRTEDAAKDPDPELLKQKGKFCKFGLCENDT NOTIONALINI	LMVVHPRAQPRTEDAAKDPDPELLKQRGRPCRFGLCERDPKSHSSACAEG		YTTSRDRKYCEDVNECATONAGCIDGCENTT COTTON OF THE FILL OF T	YTLSRDRKYCEDVNECATONHGCTLGCENTPGSYHCTCPTGFVLLFDGKQ	4 NGRESSBDN 4	401 CHELVSCPGNVSKCSHGCVLTSDGFRCICEAGSVLGIGGT					PLRPGSWECDCFPGYDLQSDRKSCAASGPQPLLLFANSQUIR
7 کا کا) (167	301	301		351	351	٠	4 (•	4		4	4

FIG. 54 (CONT.²)

501 HMHFDGTDYKVLLSRQMGMVFALDYDPVESKIYFAQTALKWIERANMDGS 550
551 ORERLITEGVDTLEGLALDWIGRRIYWTDSGKSVVGGSDLSGKHHRIIIQ 600
51
601 FRISRPRGIAVHPRARRLFWTDVGMSPRIESASLQGSDRVLIASSNLLEP 650
ERISRPRGI
(
751 CLYRNGGCEHICQESLGTARCLCREGFVKAWDGKMCLPQDYPILSGENA 799

50	99	100	109	750	0 159	800	H 209	I Н 850
1 MPWGRRPTWLLLAFLLVFLKISILSVTAWQTGNCQPGPLERSERSGTCAG 	51 PAPFLVFSQGKSISRI		67 WAIPSVIRVNKRTGQNRVRLQGSMLKPSSLVVVHPLAKPGADP			110 CLYRNGGCERICQESEGIMACE CONTROLLI		160 LSKEVTSLSNSTQAEVFDDGIESSILVIETTISSTERTIS

259	006	309	950	359	1000		4 0 0	1050	459		1100
	ARCVSDGET	_			,		360 SLDSYTCNCVIGYSGDRCQTRDLRWWELRHAGYGQKHDIMVVAVCMVALV			410 LLLLLGMWGTYYYRTRKOLSNPPKNPCDEFSGSVSSSGFDSSSGFATTAL	F1
210	851	260	901	310	0.1.)	<i>ل</i> ر	3(1001	l	4	1051

FIG. 55 (CONT.¹)

509 1150		1200			
460 PQPWEVVLEKHQDPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK 509	1101 PQPWFVVLEKHQDPKNGSLPADGTNGAVVDAGLSESLESTERT TOTAL OF ANG	510 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGFENLASLCSCOORD	1151 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLESINF VOLLINGERS	560 SCHERAPDLPRQ'I'E'FVQ 570	1201 SCHERAPDLPROTEPVK 1217

FIG. 55 (CONT.²)

1 MPWGRRPTWLLLAFLLV

259	1100	00 1 00 1		359	1200		
	1051 LLLLLGMWGTYYYRTRKQLSNPPKNPCDEPSGSVSSSGPDSSSGAAVASC	260 PQPWFVVLEKHQDPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK	1101 PQPWFVVLEKHQDPKNGSLPADGTNGAVVDAGLSPSLQLGSVHLTSWRQK	310 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG	1151 PHIDGMGTGQSCWIPPSSDRGPQEIEGNSHLPSYRPVGPEKLHSLQSANG	360 SCHERAPDLPRQTEPVQ 376	1201 SCHERAPDLPRQTEPVK 1217

FIG. 56 (CONT. 1)

1 MGAASGQRGRWPLSPPLLMLSLLVLLLQPSPAPALDPGLQPGNFSPDEAG 50
AQLFAESYNSSAEVVMFQSTVASWAHDINIIEENARREEEADVSELLE.
101 VWGRRARELIESIWQNFTDSKLRRIIGSIRTLGPANLPLAQRQYNSLLS 150
NMSRIYST
201 VGIPLKPLYQDFTAISNEAYRQDDFSDTGAFWRSWYESPSFEESLEHIYH 23U

FIG. 5.

FIG. 57 (CONT. 1)

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251	OLEPLYLNLHAYVRRALHRRYGDKYVNLRGPIPAHLLGDMWAQSWENIYD 300	
251		
301	MVVPFPDKPNLDVTSTMVQKGWNATHMFRVSEEFFTSLGLSPMPPEFWAE 350	
301	MVVPFPDKP	
351	0.2	
351		
107	.TOYKDI.	
, H		
4 O I		
451		
451	DIESDINYL	

501	RTKYQGIC	
501		
551		
551		
601		
601		
	י איז אים	
TCQ		
651	EAKADRFV	
701		
701	HTLKYGTRAKTFDVSNFQNSSIKRIIKKLQNLDRAVLPPKELEEINQ1LL 130	

FIG. 57 (CONT.²)

FIG. 57 (CONT.3)

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800	850	850	006	006	950	950	1000	-	
DMETTYSLSNICYTNGTCMPLEPDLTNMMATSRKYEELLWAWKSWRDKVG 	RAILPFFPKYVEFSNKIAKLNGYTDAGDSWRSLYESDNLEQDLEKLYQEL	RAILPFFPKYVEFSNKIAKLNGYTDAGDSWRSLYESDNLEQDLEKLYQEL	QPLYLNLHAYVRRSLHRHYGSEYINLDGPIPAHLLGNMWAQTWSNIYDLV	QPLYLNLHAYVRRSLHRHYGSEYINLDGPIPAHLLGNMWAQTWSNIYDLV	APFPSAPNIDATEAMIKQGWTPRRIFKEADNFFTSLGLLPVPPEFWNKSM	APFPSAPNIDATEAMIKQGWTPRRIFKEADNFFTSLGLLPVPPEFWNKSM			LEKPTDGREVVCHPSAWDFYNGKDFRIKQCTSVNMEDLVIAHHEMGHIQI
751	801	801	851	851	901	901		9 1	951

1235

1235

AMMNYFKPLTEWLVTENRRHGETLGWPEYNWAPNT

1201

1201

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1001	FMQYKDLPVTFREGANPGFHEAIGDIMALSVSTPKHLYSLNLLSTEGSGY	1050
1001	FMQYKDLPVTFREGANPGFHEAIGDIMALSVSTPKHLYSLNLLSTEGSGY	1050
1051		1100
1051	EYDINFLMKMALDKIAFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLRL	1100
1101		1150
1101	KYQGLCPPVP	1150
1151	•	1200
1151	AGHTGPLHKC	1200

FIG. 57 (CONT. 4)

H	MTMTLHTKASGMALLHQIQGNELEPLNRPQLKMPMERALGEVYVDNSKPT 50
_	MIMILHIKASGMALLHQIQGNELEPLNRPQLKMPMERALGEVYVDNSKPT 50
51	VFNYPEGAA
51	
7	101 FDOT NEVSPSPIMITHPPPOLSPFIHPHGOOVPYYLENEPSAYAVRDTGP 150
1) 1	
101	
151	PAFYRSNS
151	

KAFFKRSIQGHNDYMCPATNQCTIDKNRRKSCQACRLRKCY 250		RKDRRGGRMLKHKRQRDDLEGRNEMGASGDMRAANLWPSPL 300	FVGMMKGGIRKDRRGGRMLKHKRQRDDLEGRNEMGASGDMRAANLWPSPL 300			VIKHTKKNSPALSLTADQMVSALLDAEPPMIYSEYDPSKPFSEASMMGLL	TNLADRELVHMINWAKRVPG 370	INLADRELVHMINWAKKVFG 3/0
YGVWSCEGC	1 YGVWSCEGCKAFFKRSIQGE	F.VGMMKGGI	251 EVGMMKGGIRKDRRGGRML	· MOGAT,18,1698NXXTHXTV		301 VIKHTKKNSPALSLTADQM	351 TNLA	351 TNLA
201	201	· · · · · · · · · · · · · · · · · · ·	25	0))	30		

FIG. 58 (CONT. 1)

1 MVPQAHGLLLLCFLLQLQGPLGTAVFITQEEAHGVLHRQRRANSLLEELW 50 1 INVPQAHGLLLLCFLLQLQGPLGTAVFITQEEAHGVLHRQRRANSLLEELW 50 1 MVPQAHGLLLCFLLQLQGPLGTAVFITQEEAHGVLHRQRRANSLLEELW 50 51 PGSLERECNEEQCSFEEAREIFKSPERTKQFWIVYSDGDQCASNPCQNGG 100 51 PGSLERECNEEQCSFEEAREIFKSPERTKQFWIVYSDGDQCASNPCQNGG 100 101 TCQDHLKSYVCFCLLDFE
EHDESEKDGDEQVRRVTQVIMPDKYIRGKINHDIALLRLHRPVTETDYVV
PKGECPWQAVLKINGLLLCGAVLLDARWIVTAAHCFDNIRYWGNITVVMG
GAVLLDARWIVTAAHCFDNIRYWGNITVVMG 14
TCODHLKSYVCFCLLDFE
PGSLERECNEEQCSFEEAREIFKSPERTKOFWIVYSDGDQCASNPCQNGG
PGSLERECNEEQCSFEEAREIFKSPERTKQFWIVYSDGDQCASNPCQNGG
T.I.CFLLOLOGPLGTAVFITQEEAHGVLHRQRRANSLLEELW

FIG. 59 (CONT. 1)

150 200 250 250 250 300 300	
Ω	AQIIELVMTCILYVVVSGNLMYNSFPGLPVSQKSWSIIATAV
200	
200	CCYTGKILIACLYEENEDGEVVRVRDSYVAIANACCAPRFPT
150	
150	GGHDKPKITAWEAGWNVTNAIQGMFVLGLPYAILHGGYLGLF
100	
100	OMDILKSEGEPCGDEGAEAPVEGDIHYORGGAPLPPSGSKDQ
50	
20	MAILLKSKLINVAISVSNKSQAKVSGMFAKMGFQAAIUEEAVGFAHCUUL S

301	IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVL 350
301	IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVL 350
351	KGLFALVAYLTWADETKEVITDNLPGSIRAVVNLFLVAKALLSYPLPFFA 400
	•
351	KGLFALVAYLTWADETKEVITDNLPGSIRAVVNLFLVAKALLSYPLPFFA 400
401	•
401	AVEVLEKSLFQEGSRAFFPACYGGDGRLKSWELTLRCALVVFTLLMAIYV 450
451	PHFALLMGLTGSLTGAGLCFLLPSLFHLRLLWRKLLWHQVFFDVAIFVIG 500
451	PHFALLMGLTGSLTGAGLCFLLPSLFHLRLLWRKLLWHQVFFDVAIFVIG 500
	501 GICSVSGFVHSLEGLIEAYRT 521
	501 GICSVSGFVHSLEGKFAGLET 521

FIG. 61 (CONT. 1)

250	201 FKQSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY	7
250	201 FKQSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY	7
200	151 SPGSVDPLTRLVLVNAVYFRGNWDGQFDKENTEERLFKVSKNEEKPVQMM	\vdash
200	TRLVLVNAVYFRGNWDEQFDKENTEERLFKVSKNEEKPVQMM	↔
150	101 DELSSFRDSCOKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	
150	101 DFLSSFRDSCQKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	~ →
100	51 AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC	-,
100	FNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC	-,
50		
20	1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 50	

	351 ADHPFLFFIQHSKTNGILFCGR 372	
350		· · · · · · · · · · · · · · · · · · ·
350		()
300		(1
300	251 EKFVEWTRLDMMDEEEVEVSLPRFKLEESYDMESVLRNLGMTDAFELGKA 300	′ ′

FIG. 62 (CONT. 1)

351

	1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVIMGARGNIA 30
51	51 AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC 100
51	AOMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC
,	
101	DELSSERDSCOKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL
101	DFLSSFRDSCOKFYQAEMEELDFISAVEKSRKHINTWVAEKIEGALAELL
151	SPGSVDPLTRLVLVNAVYFRGNWDEQFDKENTEERLFKVSKNEEKFVQMM
151	SPGSVDPLT
201	FKOS
I)]	
201	201 FKOSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY 250

300	300	350	350	•	164/209
251 EKFVEWTRLDMMDEEEVEVSLPRFKLEESYDMESVLRNLGMTDAFELGKA	DMMDEEEVEVSLPRFKLEESYDMESVLRNLGMTDAFELGKA	301 DFSGMSQTDLSLSKVVHKSFVEVNEEGTEAAAATAAIMMMRCARFVPRFC	LSLSKVVHKSFVEVNEEGTEAAAATAAIMMMRCARFVPRFC	351 ADHPFLFFIQOR 362	

FIG. 63 (CONT. 1)

157	VGYRVPAGSGPSLPPMPSLQEVDCGSPSSSEEEGVPGSRGSPATSPHLGR 206:
207	RRPLIRSMSAAFCSILAPERQVGRAAAALMQDRHTAAGQLVQDLLTQVRD 256
51	RRPLIRSMSAAFCSLLAPERQVGRAAAALMQDRHTAAGQLVQDLLTQVRD 100
257	GORPOELEGIRQALSRARAMLSAELGPEKLVSPKRLEHVLEKSLHCSVLK 306
101	GORPQELEG
307	PLRPILAAR
151	
357	-
201	

456

LSLVLAHCDLPELLLEAEYMSELLEPSLLTGEGGYYLTSLSASLALLSGL

407

251

LSLVLAHCDLPELLLEAEYMSELLEPSLLTGEGGYYLTSLSASLALLSGL

300

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FIG. 64 (CONT. 1)

122	122 MSDASLRSTSTMERLVARGTFPVLVRTSACRSLFGPVDHEELSRELQARL 171
172	172 AELNAEDQNRWDYDFQQDMPLRGPGRLQWTEVDSDSVPAFYRETVQVGRC 221
51	AELNAEDONRWDYDFQQDMPLRGPGRLQWTEVDSDSVPAFYRETVQVGRC 100
222	RLLLAPRPVAVAVSPPLEPAAESLDGLEEAPEQLPSVPVPAPASTPPP 271
101	
272	VPVLAPAPAPAPAPVAAPVAAPVAVPVLAPAPAPAPAPAP
151	•
322	322 APAPAPAPAPAPAPOAAPQESAEQGANQGQRGQEPLADQLHSGISGRP 371
201	•

FIG. 65 (CONT. 1)

, - 	1 MEPAAGSSMEPSADWLASAAARGLVEKVRQLLEAGADPNAPNSYGRRPIQ 50
 1	
51	VMMMGSARV
51	
101	_
101	
	151 PS 152

FIG. 66

152

151

 I	
\leftarrow	MREENKGMPSGGGSDEGLASAAARGLVEKVRQLLEAGADPNGVNRFGRRA 50
51	51 IQVMMMGSARVAELLLLHGAEPNCADPATLTRPVHDAAREGFLDTLVVLH 100
51	
	137
	101 KAGAKLDVKUAWGKLFVDLAHELDGIIKUVKIKLAKELG +0.
	101 RAGARLDVRDAWGRLPVDLAEERGHRDVAGYLRTATG 137

	MKHSLNALLIFLIITSAWGGSKGPLDQLEKGGETAQSADPQWEQLNNKNL 50 	
51	SMPLLPADFHKENTVTNDWIPEGEEDDDYLDLEKIFSEDDDYIDIVDSLS 100	
51	SMPLLPADFHKENTVTNDWIPEGEEDDDYLDLEKIFSEDDDYIDIVDSLS 100	
101	VSPTDSDVSAGNILQLFHGKSRIQRLNILNAKFAFNLYRVLKDQVNTFDN 150	0
101	VSPTDSDV	0
151	IFIAPVGI	0
151	IFIAPVGISTAMGMISLGLKGETHEQVHSILHFKDFVNASSKYEITTIHN 200	0
201	LERKLTHRLERRNEGYTLRSVNDLYIQKQFPILLDFKTKVREYYFAEAQI 250	0
201	LFRKLTHR	0

	•	
251	ADFSDPAFISKTNNHIMKLTKGLIKDALENIDPATQMMILNCIYFKGSWV	300
251		300
301	301 NKFPVEMTHNHNFRLNEREVVKVSMMQTKGNFLA	334
301	NKFPVEMTHNHNFRLNEREVVKVSMMQTKGNFLAANDQELDCDILQLEYV 350	350
	•	
335	SCLLFMGRVANPSRS 349	49
451	451 QATTVTTVGFMPLSTQVRFTVDRPFLFLIYEHRTSCLLFMGRVANPSRS 499	66

FIG. 68 (CONT. 1)

1 MDPARPLGLSILLL	1 MDPARPLGLSILLLFLTEAALGDAAQEPTGNNAEICLLPLDYGPCRALLL 50
51 RYYYDRYTQSCRQF	
51 RYYYDRYTQSCRQF	RYYYDRYTQSCRQFLYGGCEGNANNFYTWEACDDACWRIEKVPKVCKLQV 100
101 SVDDOCEGSTEKY	SWILLSSMICEKFFSGGCHRNRIENRFPDEATCMGFCA 150
101 SVDDQCEGSTEKY	
	PULL DEFLY SPENFET CSANVTRYYENPRYRTCDAFTYTGCGGNDNNFVT 200
151 PKKIPSFCYSPKD	YSPKDEGLCSANVTRYYFNPRYRTCDAFTYTGCGGNDNNFVS 200
	201 VQK.MRDCA 208
	:

1 MDPARPLGLSILLLFLTEAALGDAAQEPTGNNAEICLLPLDYGPCRALLL 50
51 RYYYDRYTQSCRQFLYGGCEGNANNFYTWEACDDACWRIEKVPKVCRLQV 100 101 SVDDQCEGSTEKYFFNLSSMTCEKFFSGGCHRNRIENRFPDEATCMGFCA 150
151 PKK

FIG. 7(

	201 QSTKVPSLF 209
200	
200	151 ERFKYGGCLGNMNNFETLEECKNICEDGPNGFQVDNYGTQLNAVNNSLTP
150	
150	101 KKMCTRDNANRIIKTTLQQEKPDFCFLEEDPGICRGYITRYFYNNQTKQC
100	51 HSFCAFKADDGPCKAIMKRFFFNIFTRQCEEFIYGGCEGNQNRFESLEEC
100	51 HSFCAFKADDGPCKAIMKRFFFNIFTRQCEEFIYGGCEGNONRFESLEEC
50	
20	1 MIYTMKKVHALWASVCLLLNLAPAPLNADSEEDEEHTIITDTELPPLKLM

-1	1 MASKLILLILLLLAGURASSNPNATSSSSQUPESLQURGEGKVATTVI 50
\leftarrow	MASRLTLLTLLLLLLAGDRASSNPNATSSSSQDPESLQDRGEGKVATTVI 50
51	SKMLEVEPILEVSSLPTTNSTTNSATKITANTTDEPTTQPTTEPTTQPTI 100
51	SKMLEVEPILEVSSLPTINSTINSATKITANTIDEPTTOPTTEPTTOPTI 100
101	OPTOPTTOLPTDSPTOPTTGSFCPGPVTLCSDLESHSTEAVLGDALVDFS 150
101	OPTOPITO
151	LKLYHAFSAMKKVETNMAFSPFSIASLLTQVLLGAGENTKTNLESILSYP 200
151	151 LKLYHAFSAMKKVETNMAFSPFSIASLLTOVLLGAGENTKTNLESILSYP 200

201	KDFTCVHQALKGFTTKGVTSVSQIFHSPVDWRLLQSKSQEVLSQTSTKAR	250
201		227
		400
351) 1
228		264
		450
)1		
265		314
	MINOUVILLE IO IO IO IO IO IO IO I I I I I I I I I	500
451	FKNSVIKVPMMNSKKYPVAHFIDQILLAARVGKAKALKALITALIIIIIIIIIIIIIIIIIIIIIIIIIIII	7
315	FKNSVIKVPMMNSKKYPVAHFIDQTLKAKVGQLQLSHNLSLVILVPQNLK	007

FIG. 72 (CONT. 1)

501	HRLEDMEQALSPSVFKAIMEKLEMSKFQPTLLTLPRIKVTTSQDMLSIME 550	550
365	HRLEDMEQALSPSVFKAIMEKLEMSKFQPTLLTLPRIKVTTSQDMLSIME	414
551	KLEFFDFSYDLNLCGLTEDPDLQVSAMQHQTVLELTETGVEAAAASAISV	009
415	KLEFFDFSYDLNLCGLTEDPDLQVSAMQHQTVLELTETGVEAAAASAISV	464
	601 ARTLLVFEVQQPFLFVLWDQQHKFPVFMGRVYDPRA 636	
	465 ARTLLVFEVQQPFLFVLWDQQHKFPVFMGRVYDPRA 500	

FIG. 72 (CONT. 2)

250	FKQSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY	201
250	FKQSTFKKTYIGEIFTQILVLPYVGKELNMIIMLPDETTDLRTVEKELTY	201
200	SPGSVDPLTRLVLVNAVYFRGNWDEQFDKENTEERLFKVSKNEEKPVQMM	151
200	SPGSVDPLTRLVLVNAVYFRGNWDGQFDKENTEERLFKVSKNEEKPVQMM	151
150	DFLSSFRDSCQKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	101
150	DFLSSFRDSCQKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKIAELL	101
100	AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRMANRLFGEKSC	51
100	AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC	51
50		, ,
50	STFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA	, ,

	351 ADHPFLFFIQH 361 	
350	DFSGMSQTDLSLSKVVHKSFVEVNEEGTEAAAATAAIMMMRCARFVPRFC	301
350	DESGMSQTDLSLSKVVHKSFVEVNEEGTEAAAATAAIMMMRCARFVPRFC	301
300	-	251
300	EKFVEWTRLDMMDEEEVEVSLPRFKLEESYDMESVLRNLGMTDAFELGKA	251

FIG. 73 (CONT. 1)

~	1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 50
Н	
51	AOMAQILSE
51	AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRVANRLFGEKSC 100
101	
101	
	151 SPGSVDPLTRLVLVNAVYFRGNWDEQFDKENTEERLFKVSK 191
	141 SPCSYDDIFFERIAL VIXINAVY FRENIMPGOFOK FINERRI FKVSK 191

 1 MDVLAEANGTFALNLLKTLGKDNSKNVFFSPMSMSCALAMVYMGAKGNTA 50
51 AQMAQILSFNKSGGGGDIHQGFQSLLTEVNKTGTQYLLRMANRLFGEKSC 100
101 DFLSSFRDSCQKFYQAEMEELDFISAVEKSRKHINTWVAEKTEGKM 146

350	350	400	386	450	415	500	465
DLRDLVTT		GVDPGLAR		PLPFPRPRPFPSPRLSAPLPAGTVELVRALPLALVLHELGAGRSRAGEPL		451 RLGVGAELLVDVGQRLRRGTPWLRVHRDGPALSGPQSRALQEALVLSDRA	416 RLGVGAELLVDVGQRLRRGTPWLRVHRDGPALSGPQSRALQEALVLSDRA
301	301	351	351	401	387	45	41

FIG. 76 (CONT. 1)

482

466

501

۲	MSDASTRETSTMERLVARGTFPVLVRTSACRSLFGPVDHEELSRELOARL 50	20
4		ر ا
 1	MSDASLRSTSTMERLVARGTFPVLVRTSACRSLFGFVDHEELSNELGAANS))
	OVTHEND TO THE TOTAL TO THE TABLE OF THE TAB	96
51	AELNAEDONRWDYDFQQDMPLRGPGKLQWTE V DSDS V FALTING F C	
		96
7		

T.G. 7

1 MGAPACALALCVAVAIVAGASSESLGTEQRVVGRAAEVPGPEPGQQEQLV 50
51 FGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNAS 100
101 HEDSGAYSCRORLTORVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGA 150
151 PYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREFRGEHR 200
151 PYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREFRGEHR 200
201 IGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSP 250
201 IGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSP 250
251 HRPILOAGLPANOTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGP 300
) X

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301	DGTPYVTVI	20
301		20
		C
351	SAWLVVLPAKEKLVKADEĄGSVYAGILDSYGVGFFLFVVAAN I ACKLKS)
351	SAWLVVLP	00
401	PPKKGLGSPTVHKISRFPLKRQVSLESNASMSSNTPLVRIARLSSGEGPT 4	50
		(
401	PPKKGLGSPTVHKISRFPLKRQVSLESNASMSSNTPLVRIARLSSGEGPT 450	20
451	• •	00
		,
451	LANVSELELPADPKWELSRARLTLGKPLGEGCFGQVVMAEAIGIDKDRAA 500	00
	501 KPVTVAVKMLKDDATDKDLSDLVSEMEMMKMIGKHKNIINLL 542	
	501 KPVTVAVKMLKDDATDKDLSDLVSEMEMMKMIGKHKNIINLL 542	

FIG. 78 (CONT. 1)

1 MDPARPLGLSILLLFLTEAALGDAAQEPTGNNAEICLLPLDYGPCRALLL 50
51 RYYYDRYTQSCRQFLYGGCEGNRNNFYTWEACDDACWRIEKVPKVCRLQV 100
101 SVDDQCEGSTEKYFFNLSSMTCEKFFSGGCHRNRIENRFPDEATCMGFCA 150
151 PKKIPSFCYSPKDEGLCSANVTRYYFN 177

	VARSMGG 150 VARSMGG 150	: : : ELKVPPR 200	RLKCDEW 250	IIIIIII BRLKCDEW 250
APCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGDVAFVKHS APCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGDVAFVKHS APCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGDVAFVKHS APCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGDVAFVKHS	DEYKDCHLAQVPSHTV 	SSPHGKDLLFKDSAHG	TDECKPVKWCALSHHE	
MNQLRGKKSCHTGLGRSAGWNIPIGLLYCDLPEPRKPLEKAVANFFSGSC APCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGDVAFVKHS	TIFENLANKADRDQYELLCLDNTRKPVDEYKDCHLAQVPSHTVVARSMGG	151 KEDLIWELLNQAQEHFGKDKSKEFQLFSSPHGKDLLFKDSAHGFLKVPPR 	201 MDAKMYLGYEYVTAIRNLREGTCPEAPTDECKPVKWCALSHHERLKCDEW	
	101 TIFENLANKADR 111111111111111111111111111111111111	151 KEDLIWELLNQ? 	MDAKMYLG	

251	SVNSVGKIECVSAETTEDCIAKIMNGEADAMSLDGGFVYIAGKCGLVPVL	300
251	SVNSVGKIECVSAETTEDCIAKIMNGEADAMSLDGGFVYIAGKCGLVPVL	300
		0
301	AENYNKSDNCEDTPEAGYFAVAVVKKSASDLTWDNLKGKKSCHTAVGKIA	220
(350
7 O C		
351	GWNI PMGLLYNKINHCEP	368
		(
351	GWNIPMGLLYNKINHCRFDEFFSEGCAPGSKKDSSLCKLCMGSGLNLCEP	400
		7
369	NNKEGYYGYTGAFRCLVEKGDVAFVKHQTVPQNTGGKNPDPWAKNLNEKD	4 T 8
		((
401	NNKEGYYGYTGAFRCLVEKGDVAFVKHQTVPQNTGGKNPDPWAKNLNEKU	450
		(
419		468
		((
451		200

FIG. 80 (CONT. 1)

518	55(
9 GSNVTDCSGNFCLFRSETKDLLFRDDTVCLAKLHDRNTYEKYLGEEYVKA	1 GSNVTDCSGNFCLFRSETKDLLFRDDTVCLAKLHDRNTYEKYLGEEYVKA
46	501

519 VGNLRKCSTSSLLEACTFRRP 539

551 VGNLRKCSTSSLLEACTFRRP 571

FIG. 80 (CONT. 2)

50 50 MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCAELLRSQTEKHK

	37 NGFQVDNYGTQLNAVNNSLTPQSTKVPSLFEFHGPSWCLTPADRGLCRAN 86	
- N 80 80		0
Ē	87 FNRFYYNSVIGKCRPFKYSGCGGNENNFTSKQECLRACKKGFIQRISKGG 136	
i —		σ
Ι	30 ENRFYYNSVIGKCRPFKYSGCGGNENNFTSKQECLKACKNGFIQKLSNGG 277	`
	137 LIKTKRKKKORVKIAYEEIFVKNM 161	
	280 LIKTKRKKKORVKIAYEEIFVKNM 304	

ENFRKKEVLCPELPPGSAKRALPTCTSASPPQKKKPLDGEYFTLKIRGRK 283 RPILTIITLEDSSGNLLGRDSFEVRVCACPGRDRRTEE RPILTIITLEDSSGNLLGRDSFEVRVCASPGRDPRTEE 246

151 KVGPDSD 157 ||||||| 384 KVGPDSD 390

. 20 283

RPILTIITLEDSSGNLLGRDSFEVRVCACPGRDRRTEE

246

13

RPILTIITLEDSSGNLLGRDSFEVRVCASPGRDPRTEE

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51 E	ENFRKKEVLCPELPPGSAKRALPTCTSASPPQKKKPLDGEYFTLKIRGRK 100 	0 0 33
101	101 RFEMFRELNEALELKDAHATEESGDSRAHSSYLKTKKGQSTSRHKKTMVK 150	20
334		33
	151 KVGPDSD 157 	

FIG. 84

384 KVGPDSD 390

1 MGAASGORGRWPLSPPLLMLSLLVLLLOPSPAPALDPGLOPGNFSPDEAG 50
51 AQLFAESYNSSAEVVMFQSTVASWAHDTNITEENARRQEEAALVSQEFAE 100
_ 01
101 VWGKKAKELYESIWQNFTDSKLRRIIGSIRTLGPANLPLAQRQQYNSLLS 150
101 VWGKKAKELYESIWQNFTDSKLRRIIGSIRTLGPANLPLAQRQQYNSLLS 150
151 NMSRIYSTGKVCFPNKTATCWSLDPELTNILASSRSYAKLLFAWEGWHDA 200
151 NMSRIYSTGKVCFPNKTATCWSLDPELTNILASSRSYAKLLFAWEGWHDA 200
201 VGIPLKPLYQDFTAISNEAYRQDDFSDTGAFWRSWYESPSFEESLEHIYH 250
201 VGIPLKPLYQDFTAISNEAYRQDDFSDTGAFWRSWYESPSFEESLEHIYH 250

FIG. 8.

200	DIESDINYLLKMALEKIAFLPFGYLVDQWRWGVFSGRTPPSRYNFDWWYL	451
500	DIESDINYLLKMALEKIAFLPFGYLVDQWRWGVFSGRTPPSRYNFDWWYL	451
450	•	401
450	OYYLQYKDLHVSLRRGANPGFHEAIGDVLALSVSTPAHLHKIGLLDHVTN	401
400	SMLEKPTDG	351
400	SMLEKPTDGREVVCHASAWDFYNRKDFRIKQCTRVTMEQLATVHHEMGHV	351
350	MVVPFPDKPNLDVTSTMVQKGWNATHMFRVSEEFFTSLGLSPMPPEFWAE	301
350	,	301
300	QLEPLYLNLHAYVRRALHRRYGDKYVNLRGPIPAHLLGDMWAQSWENIYD	251
300	_	251

FIG. 85 (CONT. 1)

501 RTKYQGICPPVARNETHFDAGAKFHIPNVTPYIRYFVSFVLQFQFHQALC 550
--

801	RAILPEFPK	850
1 n		850
T 0 8	KALLFEFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF	
851	QPLYLNLHA	
851	QPLYLNLHA	
901	• •	950
901	APFPSAPNI	950
L		1000
45T	LENY LOGRE V CALE SANDE LINGUISTICK CO. T	(
951	LEKPTDGREVVCHPSAWDFYNGKDFRIKQCTSVNMEDLVIAHHEMGHIQY	0001
,	YPSPAPS TIN TRY THACTRICATION TO THE CONTROL OF THE	1050
1001	FMQYKDLPV	L L
1001	FMOYKDLPV	1020 1
	•	

$FIG.85(CONT.^3)$

1051	1051 EYDINFLMKMALDKIAFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLKL 1100	0011
1051	EYDINFLMKMALDKIAFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLRL	1100
1101	KYQGLCPPVPRSQGDFDPGSKFHVPANVPYVRYFVSFIIQFQFHEALCRA	1150
1101	KYQGLCPPVPRSQGDFDPGSKFHVPANVPYVRYFVSFIIQFQFHEALCRA	1150
τ L τ	. SASMULT THEODY TANKET TANKET TANKET TO SEE THEODY	1200
T	AGHTGFLARCOT 1 QOREAGNADADAMA	f
1151	AGHTGPLHKCDIYQSKEAGKLLADAMKLGYSKPWPEAMKLITGQPNMSAS	1200
	1201 AMMNYFKPLTEWLVTENRRHGETLGWPEYNWAPNT 1235	

FIG. 85 (CONT. 4)

I MI	MTMTLHTKASGMALLHQIQGNELEPLNRPQLKMPMERALGEVYVDNSKPT 50
1 M.	
51 VI	VENYPEGAAYEFNAAAAAAAAAASAPVYGQSGIAYGPGSEAAAFSANSLGA 100
51 V	VENYPEGAAYEFNAAAAAAAAAASAPVYGQSGIAYGPGSEAAAFSANSLGA 100
101 F	FPOLNSVSPSPLMLLHPPPQLSPFLHPHGQQVPYYLENEPSAYAVRDTGP 150
101 F	TOTANATTE STANTALIA (QV) TOTANATILA PROTOSTALIA (PROTOSTALIA).
151 E	PAFYRSNSDNRRONGRERLSSSNEKGNMIMESAKETRYCAVCNDYASGYH 200
	1 1 1 1 1 1 1 1 1 1
151 E	PAFYRSNSDNRRONGRERLSSSNEKGNMIMESAKEINICAVCKUIISSII
	08C VONGIOOROOMAGINATEROOMERICA .
201	4
201	YGVWSCEGCKAFFKRSIQGHNDYMCPATNQCTIDKNKKKSCQACKLKKCT 233

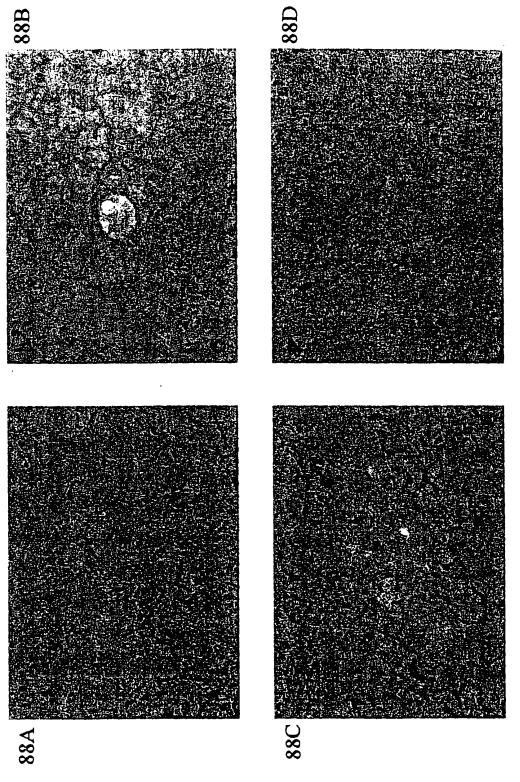
300	300		350	350			
WWW.Day	TOSOMINA CAMORS & CAM	251 EVGMMKGGIRKDRRGGRMLKHKKQKUULEGKNEMGASSULLELENSTERS	/1/1011/17:	301 VIKHTANDFALGERINGERINGERINGERINGERINGERINGERINGERIN	301 VIKHTKKNSPALSLTADOMVSALLDAEPPMLISEIDESNELSLINGER	351 TNLADRELVHMINWAKRVPGGNSL 374	351 TNLADRELVHMINWAKRVPGFGDL 3/4
C	7	(1)	,	• ,	V-)		

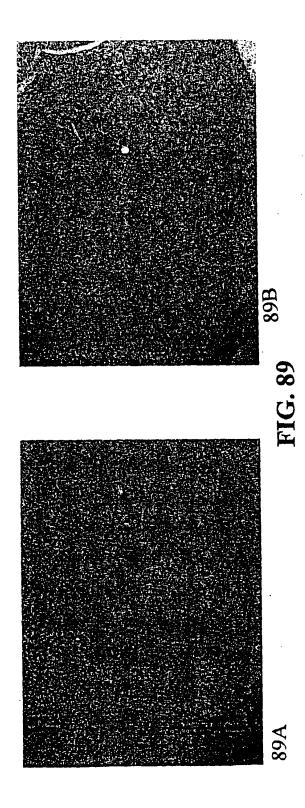
FIG.86(Cont.1)

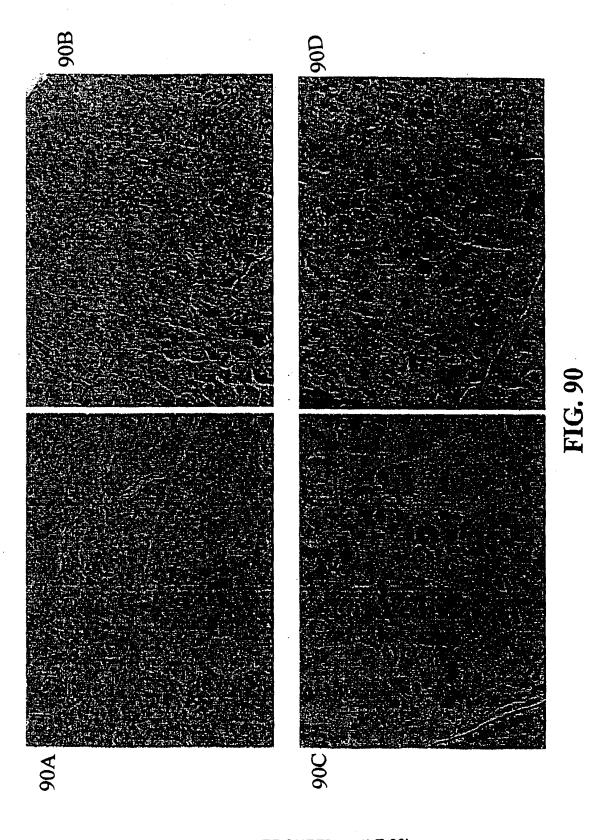
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	DQ 100	00
51 DFEHRQGLQMDILKSEGEPCGDEGAEAPVEGDIHYQRGGAPLPPSGSKDQ	 DQ 100	00
101 AVGAGGEFGGHDKPKITAWEAGWNVTNAIQGMFVLGLPYAILHGGYLGLF		150
101 AVGAGGEFGGHDKPKITAWEAGWNVTNAIQGMFVLGLPYAILHGGYLGLF		150
TOTALLE TOTALLE TO TABLE NEIGHT TO TABLE TO THE TOTALLE TO THE TOTA		200
		(
151 LIIFAAVVCCYTGKILIACLYEENEDGEVVRVRDSYVAIANACCAPRFPT		200
201 LGGRUUNVAOIIELVMTCILYVVVSGNLMYNSFPGLPVSQKSWSIIATAV		250
201 1.GGRUVNVAOIIELVMTCILYVVVSGNLMYNSFPGLPVSQKSWSIIATAV		250

448		
448		
400	351 KGLFALVAYLTWADETKEVITDNLPGSIRAVVNLFLVAKALLSYPLPFFA	
400	351 KGLFALVAYLTWADETKEVITDNLPGSIRAVVNLFLVAKALLSYPLPFFA	
350	301 IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVL	
350	301 IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVL	
300	251 LLPCAFLKNLKAVSKFSLLCTLAHFVINILVIAYCLSRARDWAWEKVKFY	
300	251 T. PCAFTKNI,KAVSKFSLLCTLAHFVINILVIAYCLSRARDWAWEKVKFY 300	

FIG. 87 (CONT. 1)







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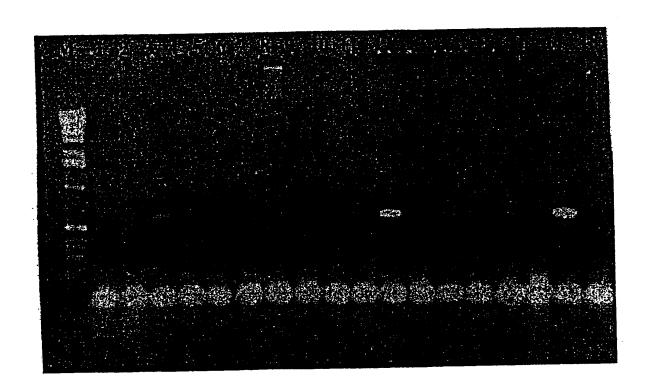
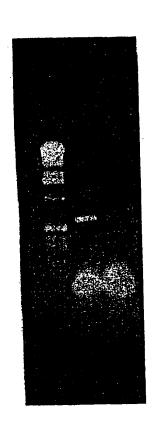


FIG. 91A

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Liver RT+ Liver RT-Skin RT+ Skin RT-Thyroid RT+ Thyroid RT-Bone marrow RT+ Bone marrow RT-Salivary gland RT+ Salivary gland RT-Lung RT+ Lung RT-Heart RT+ Heart RT-Thymus RT+ Thymus RT-Spleen RT+ Spleen RT-Brain RT+ Brain RT-

PCT/IL00/00766

FIG. 91B

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Thr Ala Ile Asn Leu Gly Leu Lys Lys Glu Pro Asn Val Ala A	rg Val
Gly Ser Val Ala Ile Lys Leu Cys Asn Leu Leu Lys Ile Ala P	ro Pro
Ala Val Cys Gln Ser Ile Val His Leu Phe Glu Asp Asp Met V 130 135 140	al Glu
Val Trp Arg Arg Ser Val Leu Ser Pro Ser Glu Ala Cys Gly I 145 150 155	leu Leu 160
Leu Gly Ser Thr Cys Gly His Trp Asp Ile Phe Ser Ser Trp A	Asn Ile 175
Ser Leu Pro Thr Val Pro Lys Pro Pro Pro Lys Pro Pro Ser	Pro Pro
Ala Pro Gly Ala Pro Val Ser Arg Ile Leu Phe Leu Thr Asp 195 200 205	Leu His
Trp Asp His Asp Tyr Leu Glu Gly Thr Asp Pro Asp Cys Ala 210 215 220	Asp Pro
Leu Cys Cys Arg Arg Gly Ser Gly Leu Pro Pro Ala Ser Arg 225 230 235	Pro Gly 240
Ala Gly Tyr Trp Gly Glu Tyr Ser Lys Cys Asp Leu Pro Leu 245 250	Arg Thr 255
Leu Glu Ser Leu Leu Ser Gly Leu Gly Pro Ala Gly Pro Phe 260 265 270	Asp Met
Val Tyr Trp Thr Gly Asp Ile Pro Ala His Asp Val Trp His	Gln Thr

275

PC.1/1F00/00/00/00

285

Arg Gln Asp Gln Leu Arg Ala Leu Thr Thr Val Thr Ala Leu Val Arg 295

280

Lys Phe Leu Gly Pro Val Pro Val Tyr Pro Ala Val Gly Asn His Glu 310

Ser Thr Pro Val Asn Ser Phe Pro Pro Pro Phe Ile Glu Gly Asn His 330

Ser Ser Arg Trp Leu Tyr Glu Ala Met Ala Lys Ala Trp Glu Pro Trp 345

Leu Pro Ala Glu Ala Leu Arg Thr Leu Arg Ile Gly Gly Phe Tyr Ala 360

Leu Ser Pro Tyr Pro Gly Leu Arg Leu Ile Ser Leu Asn Met Asn Phe 375

Cys Ser Arg Glu Asn Phe Trp Leu Leu Ile Asn Ser Thr Asp Pro Ala 395 390

Gly Gln Leu Gln Trp Leu Val Gly Glu Leu Gln Ala Ala Glu Asp Arg 410

Gly Asp Lys Val His Ile Ile Gly His Ile Pro Pro Gly His Cys Leu 425

Lys Ser Trp Ser Trp Asn Tyr Tyr Arg Ile Val Ala Arg Tyr Glu Asn 440

Thr Leu Ala Ala Gln Phe Phe Gly His Thr His Val Asp Glu Phe Glu 455

Val Phe Tyr Asp Glu Glu Thr Leu Ser Arg Pro Leu Ala Val Ala Phe 475 470

Leu Ala Pro Ser Ala Thr Thr Tyr Ile Gly Leu Asn Pro Leu Val Ser 49,0

Glu Ala Glu Gly Ser Leu Pro Tyr Pro Gly Val Gly Gly Ile Gly Glu 505

Gly Gly Trp Ser Gln Ser Leu Gln Ser Met Gly Arg Met Cys Gly Pro

Ser Leu Glu Leu Pro Leu Leu Leu Ala Pro Pro Val Ser Pro Thr Ser 535

Leu Ala Gly Tyr Arg Val Tyr Gln Ile Asp Gly Asn Tyr Ser Gly Ser 550

Ser His Val Val Leu Asp His Glu Thr Tyr Ile Leu Asn Leu Thr Gln

Ala Asn Ile Pro Gly Ala Ile Pro His Trp Gln Leu Leu Tyr Arg Ala 585

Arg Glu Thr Tyr Gly Leu Pro Asn Thr Leu Pro Thr Ala Trp His Asn 600

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Leu Val Tyr Arg Met Arg Gly Asp Met Gln Leu Phe Gln Thr Phe Trp

Phe Leu Tyr His Lys Gly His Pro Pro Ser Glu Pro Cys Gly Thr Pro 635 630 625

Cys Arg Leu Ala Thr Leu Cys Ala Gln Leu Ser Ala Arg Ala Asp Ser 650

Pro Ala Leu Cys Arg His Leu Met Pro Asp Gly Ser Leu Pro Glu Ala

Gln Ser Leu Trp Pro Arg Pro Leu Phe Cys

<210> 90

<211> 515

<212> PRT

<213> Homo sapiens

<400> 90

Leu Leu Leu Gly Phe Leu Leu Val Ser Leu Glu Ser Thr Leu Ser

Ile Pro Pro Trp Glu Ala Pro Lys Glu His Lys Tyr Lys Ala Glu Glu

His Thr Val Val Leu Thr Val Thr Gly Glu Pro Cys His Phe Pro Phe

Gln Tyr His Arg Gln Leu Tyr His Lys Cys Thr His Lys Gly Arg Pro

Gly Pro Gln Pro Trp Cys Ala Thr Thr Pro Asn Phe Asp Gln Asp Gln

Arg Trp Gly Tyr Cys Leu Glu Pro Lys Lys Val Lys Asp His Cys Ser

Lys His Ser Pro Cys Gln Lys Gly Gly Thr Cys Val Asn Met Pro Ser

Gly Pro His Cys Leu Cys Pro Gln His Leu Thr Gly Asn His Cys Gln 120

Lys Glu Lys Cys Phe Glu Pro Gln Leu Leu Arg Phe Phe His Lys Asn 135

Glu Ile Trp Tyr Arg Thr Glu Gln Ala Ala Val Ala Arg Cys Gln Cys 155 145

Lys Gly Pro Asp Ala His Cys Gln Arg Leu Ala Ser Gln Ala Cys Arg

Thr Asn Pro Cys Leu His Gly Gly Arg Cys Leu Glu Val Glu Gly His 180

Arg Leu Cys His Cys Pro Val Gly Tyr Thr Gly Pro Phe Cys Asp Val

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Asp	Th:		ys	Ala	Ser	Cys	ту 21	r A 5	sp (Gly	Ar	g	Gly	Leu 220	Ser	ту	r A	Arg	Gly	Y
Leu 225	Al	a A	ırg	Thr	Thr	Le:	ي Se ک	er G	ly	Ala	Pı	ro	Cys 235	Gln	Pro	Tr	p F	Ala	Se:	r 0
Glu	Al	a T	hr	Tyr	Arg 245	As:	n Va	al T	hr	Ala	G. 2	lu 50	Gln	Ala	Arg	g As	sn '	Trp 255	Gl	У
Leu	Gl	у (Gly	His 260	Ala	a Ph	e Cy	ys l	Arg	Asn 265	P	ro	Asp	Asr	a Ası	2 I	le / 70	Arg	Pr	0
Trp	, СУ	'S	Phe 275	Val	Le	ι As	n A	rg i	Asp 280	Arç	g L	eu	Ser	Trp	0 G1 28	u T 5	yr	Cys	As	p
Leu		.a 90	Gln	Cys	Gl	n Th	r P 2	ro 95	Thr	Glı	n A	la	Ala	300	o Pr	о Т	hr	Pro	Vá	ıl
305	5			Lei		3.	LU						J 1 0							
				Pro	32	5					•	,,,,								
				Al. 34	0					74	J				•					
			35						300	,										
	3	370		l Gl				313						-						
38	35			u Ty		-	390						-	. •						
				p Vá	4	05						7.1	!							
					20					7	23									
			43	ro C 35 .					44	·						_				
		45	0	er P				40	5				**							
4	65			sp A			4/0						•	, •						
				ys I		485						7	J 0							
(Cys	Gl	n V	al A	Ala 500	Gly	Trp	Gl	уН	is	Glr 505	n P 5	he (ilu i	Ala	Ser	51	eu P LO	ro	Met

Lys Leu Asn 515

<pre><210> 91 <211> 775 <212> PRT <213> Homo sapiens</pre>
<pre><400> 91 Met Ala Arg Leu Gly Asn Cys Ser Leu Thr Trp Ala Ala Leu Ile Ile</pre>
Leu Leu Leu Pro Gly Ser Leu Glu Glu Cys Gly His Ile Ser Val Ser 20 25 30
Ala Pro Ile Val His Leu Gly Asp Pro Ile Thr Ala Ser Cys Ile Ile 35
Lys Gln Asn Cys Ser His Leu Asp Pro Glu Pro Gln Ile Leu Trp Arg 50 60
Leu Gly Ala Glu Leu Gln Pro Gly Gly Arg Gln Gln Arg Leu Ser Asp 65 70 75 80
Gly Thr Gln Glu Ser Ile Ile Thr Leu Pro His Leu Asn His Thr Gln 85 90 95
Ala Phe Leu Ser Cys Cys Leu Asn Trp Gly Asn Ser Leu Gln Ile Leu 100 100 115
Asp Gln Val Glu Leu Arg Ala Gly Tyr Pro Pro Ala Ile Pro His Asn 115 120 125
Leu Ser Cys Leu Met Asn Leu Thr Thr Ser Ser Leu Ile Cys Gln Trp 130 135 140
Glu Pro Gly Pro Glu Thr His Leu Pro Thr Ser Phe Thr Leu Lys Ser 145 150 155 160
Phe Lys Ser Arg Gly Asn Cys Gln Thr Gln Gly Asp Ser Ile Leu Asp. 175
Cys Val Pro Lys Asp Gly Gln Ser His Cys Cys Ile Pro Arg Lys His
Leu Leu Tyr Gln Asn Met Gly Ile Trp Val Gln Ala Glu Asn Ala 195 200 205
Leu Gly Thr Ser Met Ser Pro Gln Leu Cys Leu Asp Pro Met Asp Val 210 215 220
Val Lys Leu Glu Pro Pro Met Leu Arg Thr Met Asp Pro Ser Pro Glu 225 230 235 240
Ala Ala Pro Pro Gln Ala Gly Cys Leu Gln Leu Cys Trp Glu Pro Trp 245 250 255
Gln Pro Gly Leu His Ile Asn Gln Lys Cys Glu Leu Arg His Lys Pro 260 265 270
Gln Arg Gly Glu Ala Ser Trp Ala Leu Val Gly Pro Leu Pro Leu Glu 285

Ala	Leu 290	Gln	Tyr	Glu	Leu	Cys 295	Gly	Leu	Leu	Pro	Ala ' 300	Thr .	Ala	Tyr	Thr
Leu 305	Gln	Ile	Arg	Cys	Ile 310	Arg	Trp	Pro	Leu	Pro 315	Gly	His	Trp	Ser .	Asp 320
Gly	Ala	Ile	Leu	Pro 325	Leu	Cys	Asn	Thr .	Thr 330	Glu	Leu	Ser	Cys	Thr 335	Phe
His	Leu	Pro	Ser 340	Glu	Ala	Gln	Glu	Val 345	Ala	Leu	Val	Ala	Tyr 350	Asn	Ser
Ala	Gly	Thr 355	Ser	Arg	Pro	Thr	Pro 360	Val	Val	Phe	Ser	Glu 365	Ser	Arg	Gly
Pro	Ala 370	Leu	Thr	Arg	Leu	His 375	Ala	Met	Ala	Arg	Asp 380	Pro	His	Ser	Leu
Trp 385	Val	Gly	Trp	Glu	Pro 390	Pro	Asn	Pro	Trp	Pro 395	Gln	Gly	Tyr	Val	Ile 400
Glu	Trp	Gly	Leu	Gly 405	Pro	Pro	Ser	Ala	Ser 410	Asn	Ser	Asn	Lys	Thr 415	Trp
Arg	Met	Glu	Gln 420		Gly	Arg	Ala	Thr 425	Gly	Phe	Leu	Leu	Lys 430	Glu	Asn
Ile	Arg	Pro 435		Gln	Leu	Tyr	Glu 440	Ile	Ile	Val	Thr	Pro 445	Leu	Tyr	Gln
Asp	Thr 450		Gly	Pro	Ser	Gln 455	His	Val	Tyr	Ala	Tyr 460	Ser	Gln	Glu	Met
Ala 465		Ser	His	Ala	Pro 470		Leu	His	Leu	Lys 475	His	Ile	Gly	Lýs	Thr 480
				485					490					495	
			500)				505	ı				510		Ser
Phe	e Sei	515		e Lev	a Asn	n Ala	Ser 520	Ser	Arg	, Gly	Phe	Val 525	Leu	His	Gly
Lei	3 Glv 530		o Ala	a Sei	c Leu	Tyr 535		: Ile	His	. Leu	Met 540	Ala	Ala	Ser	Gln
Al: 54		y Al	a Thi	r Ası	n Sei 550		c Val	. Leu	1 Thr	555	Met	Thr	Leu	Thr	Pro 560
Gl	u Gl	y Se	r Gl	u Lei 56		s Ile	e Ile	e Lei	3 Gly 570	y Leu O	ı Phe	: Gly	/ Leu	Leu 575	Leu
Le	u Le	u Th	r Cy 58		u Cy:	s Gl	y Thi	585	a Try	p Lev	ı Cys	Cys	590	Pro	Asn
Ar	g Ly	s As 59		o Le	u Tr	p Pr	o Se:	r Vai	l Pr	o, As <u>r</u>	Pro	Ala 605	a His	s Ser	Ser
Le	u Gl	y Se	r Tr	p Va	l Pr	o Th	r Il	e Me	t Gl	u Gl	u Asp	Ala	a Phe	e Glr	Leu

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620 615 610 Pro Gly Leu Gly Thr Pro Pro Ile Thr Lys Leu Thr Val Leu Glu Glu 635 630 Asp Glu Lys Lys Pro Val Pro Trp Glu Ser His Asn Ser Ser Glu Thr 650 645 Cys Gly Leu Pro Thr Leu Val Gln Thr Tyr Val Leu Gln Gly Asp Pro Arg Ala Val Ser Thr Gln Pro Gln Ser Gln Ser Gly Thr Ser Asp Gln 680 675 Val Leu Tyr Gly Gln Leu Leu Gly Ser Pro Thr Ser Pro Gly Pro Gly 695 His Tyr Leu Arg Cys Asp Ser Thr Gln Pro Leu Leu Ala Gly Leu Thr Pro Ser Pro Lys Ser Tyr Glu Asn Leu Trp Phe Gln Ala Ser Pro Leu 730 Gly Thr Leu Val Thr Pro Ala Pro Ser Gln Glu Asp Asp Cys Val Phe 745 Gly Pro Leu Leu Asn Phe Pro Leu Leu Gln Gly Ile Arg Val His Gly 760 Met Glu Ala Leu Gly Ser Phe . 770 <210> 92 <211> 873 <212> PRT <213> Homo sapiens Met Ala Arg Leu Gly Asn Cys Ser Leu Thr Trp Ala Ala Leu Ile Ile Leu Leu Pro Gly Ser Leu Glu Glu Cys Gly His Ile Ser Val Ser Ala Pro Ile Val His Leu Gly Asp Pro Ile Thr Ala Ser Cys Ile Ile Lys Gln Asn Cys Ser His Leu Asp Pro Glu Pro Gln Ile Leu Trp Arg Leu Gly Ala Glu Leu Gln Pro Gly Gly Arg Gln Gln Arg Leu Ser Asp Gly Thr Gln Glu Ser Ile Ile Thr Leu Pro His Leu Asn His Thr Gln Ala Phe Leu Ser Cys Cys Leu Asn Trp Gly Asn Ser Leu Gln Ile Leu 105 Asp Gln Val Glu Leu Arg Ala Gly Tyr Pro Pro Ala Ile Pro His Asn

		115					120					125			
Leu	Ser 130	Cys	Leu	Met	Asn	Leu 135	Thr	Thr	Ser	Ser	Leu 140	Ile	Cys	Gln	Trp
Glu 145	Pro	Gly	Pro	Glu	Thr 150	His	Leu	Pro	Thr	Ser 155	Phe	Thr	Leu	Lys	Ser 160
Phe	Lys	Ser	Arg	Gly 165	Asn	Cys	Gln	Thr	Gln 170	Gly	Asp	Ser	Ile	Leu 175	Asp
Cys	Val	Pro	Lys 180	Asp	Gly	Gln	Ser	His 185	Cys	Cys	Ile	Pro	Arg 190	Lys	His
Leu	Leu	Leu 195	Tyr	Gln	Asn	Met	Gly 200	Ile	Trp	Val	Gl'n	Ala 205	Glu	Asn	Ala
Leu	Gly 210	Thr	Ser	Met	Ser	Pro 215	Gln	Leu	Суѕ	Leu	Asp 220	Pro	Met	Asp	Val
Val 225	Lys	Leu	Glu	Pro	Pro 230	Met	Leu	Arg	Thr	Met 235	Asp	Pro	Ser	Pro	Glu 240
Ala	Ala	Pro	Pro	Gln 245	Ala	Gly	Cys	Leu	Gln 250	Leu	Cys	Trp	Glu	Pro 255	Trp
			260	His				265					270		
		275		Ala			280					285			
Ala	Leu 290	Gln	Tyr	Glu	Leu	Cys 295	Gly	Leu	Leu	Pro	Ala 300	Thr	Ala	Tyr	Thr
305				Cys	310					315					320
•				Leu 325					330					335	
			340	Trp				345					350		
		355		Lys			360					365			
	370	_		Val		375					380				
385			_	Asn	390					395					400
Ser	Glu	Ala	Gln	Glu 405	Val	Ala	Leu	Val	Ala 410		Asn	Ser	Ala	Gly 415	Thi
	Ĩ		420					425					430		
Thr	Arg	Leu 435	His	Ala	Met	Ala	Arg 440	Asp	Pro	His	Ser	Leu 445		Val	Gly

Trp	Glu 450	Pro	Pro	Asn	Pro	Trp 455	Pro	Gln	Gly	Tyr	Val 460	Ile	Glu	Trp	Gly
Leu 465	Gly	Pro	Pro	Ser	Ala 470	Ser	Asn	Ser	Asn	Lys 475	Thr	Trp	Arg	Met	Glu 480
Gln	Asn	Gly	Arg	Ala 485	Thr	Gly	Phe	Leu	Leu 490	Lys	Glu	Asn	Ile	Arg 495	Pro
Phe	Gln	Leu	Tyr 500	Glu	Ile	Ile	Val	Thr 505	Pro	Leu	Tyr	Gln	Asp 510	Thr	Met
Gly	Pro	Ser 515	Gln	His	Val	Tyr	Ala 520	Tyr	Ser	Gln	Glu	Met 525	Ala	Pro	Ser
His	Ala 530	Pro	Glu	Leu	His	Leu 535	Lys	His	Ile	Gly	Lys 540	Thr	Trp	Ala	Gln
Leu 545	Glu	Trp	Val	Pro	Glu 550	Pro	Pro	Glu	Ļeu	Gly 555	Lys	Ser	Pro	Leu	Thr 560
His	Tyr	Thr	Ile	Phe 565	Trp	Thr	Asn	Ala	Gln 570	Asn	Gln	Ser	Phe	Cys 575	Glu
Ser	Xaa	Leu	Ser 580	Ser	Pro	Thr	Ala	Pro 585	Glu	Gly	Leu	Glu	Gly 590	Gly	Ala
Gln	Leu	Pro 595	Arg	Arg	Xaa	Phe	Thr 600	Ile	Gln	Ala	Tyr	Ala 605	Asp	Arg	Thr
Pro	Leu 610	Pro	Ala	Ala	Ile	Leu 615	Asn	Ala	Ser	Ser	Arg 620	Gly	Phe	Val	Leu
His 625	_	Leu	Glu	Pro	Ala 630	Ser	Leu	Tyr	His	Ile 635	His	Leu	Met	Ala	Ala 640
Ser	Gln	Ala	Gly	Ala 645	Thr	Asn	Ser	Thr	Val 650		Thr	Leu	Met	Thr 655	Leu
.Thr	Pro	Glu	Gly 660	Ser	Glu	Leu	His	Ile 665	Ile	Leu	Gly	Leu	Phe 670	Gly	Leu
Leu	Leu	Leu 675		Thr	Cys	Leu	Cys 680		Thr	Ala	Trp	Leu 685		Cys	Ser
Pro	Asn 690		Lys	Asn	Pro	Leu 695		Pro	Ser	Val	Pro 700		Pro	Ala	His
Ser 705		Leu	Gly	Ser	Trp 710		Pro	Thr	lle	Met 715	Glu	Glu	Asp	Ala	720
Glr	ı Leu	Pro	Gly	Leu 725		Thr	Pro	Pro	730		Lys	Leu	Thr	Val 735	Lev
Glu	ı Glu	Asp	740	Lys	Lys	Pro	Val	Pro 745		Glu	Ser	His	750	Ser	Ser
Glu	i Thr	Cys 755		/ Let	Pro	Thr	Leu 760		Glr	Thr	Tyr	Val	. Leu	Gln	Gly

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Asp Pro Arg Ala Val Ser Thr Gln Pro Gln Ser Gln Ser Gly Thr Ser 775 Asp Gln Val Leu Tyr Gly Gln Leu Leu Gly Ser Pro Thr Ser Pro Gly 795 790 Pro Gly His Tyr Leu Arg Cys Asp Ser Thr Gln Pro Leu Leu Ala Gly Leu Thr Pro Ser Pro Lys Ser Tyr Glu Asn Leu Trp Phe Gln Ala Ser 825 Pro Leu Gly Thr Leu Val Thr Pro Ala Pro Ser Gln Glu Asp Asp Cys Val Phe Gly Pro Leu Leu Asn Phe Pro Leu Leu Gln Gly Ile Arg Val 855 His Gly Met Glu Ala Leu Gly Ser Phe 870 <210> 93 <211> 837 <212> PRT <213> Homo sapiens <400> 93 Met Gln Lys Ile Met His Ile Ser Val Leu Leu Ser Pro Val Leu Trp Gly Leu Ile Phe Gly Val Ser Ser Asn Ser Ile Gln Ile Gly Gly Leu 25 Phe Pro Arg Gly Ala Asp Gln Glu Tyr Ser Ala Phe Arg Val Gly Met Val Gln Phe Ser Thr Ser Glu Phe Arg Leu Thr Pro His Ile Asp Asn Leu Glu Val Ala Asn Ser Phe Ala Val Thr Asn Ala Phe Cys Ser Gln 70 Phe Ser Arg Gly Val Tyr Ala Ile Phe Gly Phe Tyr Asp Lys Lys Ser Val Asn Thr Ile Thr Ser Phe Cys Gly Thr Leu His Val Ser Phe Ile 105 Thr Pro Ser Phe Pro Thr Asp Gly Thr His Pro Phe Val Ile Gln Met Arg Pro Asp Leu Lys Gly Ala Leu Leu Ser Leu Ile Glu Tyr Tyr Gln 135 Trp Asp Lys Phe Ala Tyr Leu Tyr Asp Ser Asp Arg Gly Leu Ser Thr 155 150 Leu Gln Ala Val Leu Asp Ser Ala Ala Glu Lys Lys Trp Gln Val Thr 170 165

Ala	Ile	Asn	Val 180	Gly	Asn	Ile	Asn	Asn 185	Asp	Lys	Lys	Asp	Glu 190	Met	Tyr
Arg	Ser	Leu 195	Phe	Gln	Asp	Leu	Glu 200	Leu	Lys	Lys	Glu	Arg 205	Arg	Val	Ile
Leu	Asp 210		Glu	Arg	Asp	Lys 215	Val	Asn	Asp	Ile	Val 220	Asp	Gln	Val	Ile
225					Val 230					233					
				245					230						
			260)	Ile			265					2,0		
		275	ò				280	,				200			Ala
	290)				295	•				300	,			Val
305	ı				310)				21.	,				Glu 320
				32	5				رر	J		•			
			34	0				34	5					-	L Gln
•		35	5				36	U				50	•		s Arg
	37	0				31	5				50	Ū			o Arg
38	5				39	U				,					u Thr 400
				4 ()5				4.	LU					
			4	20				4.	25				• •	, ,	s Asn
		4	35				4	40				7	1.5		l Asp
	4	50				4 :	55				7	00			eu Thr
4	65				4	70				7	, 5				ys Ile 480
				4	85				4	90				_	le Ala 95
I	le A	Ala E	Pro I	Jeu 1	hr I	le T	hr L	eu V	al P	rg G	lu G	lu V	al I	ıe A	sp Phe

			500					505					510		
Ser	Lys	Pro 515	Phe	Met	Ser	Leu	Gly 520	Ile	Ser	Ile	Met	Ile 525	Lys	Lys	Pro
Gln	Lys 530	Ser	Lys	Pro		Val 535	Phe	Ser	Phe	Leu	Asp 540	Pro	Leu	Ala	Tyr
Glu 545	Ile	Trp	Met	Cys	Ile 550	Val	Phe	Ala	Tyr	Ile 555	Gly	Val	Ser	Val	Val 560
Leu	Phe	Leu	Val	Ser 565	Arg	Phe	Ser	Pro	Tyr 570	Glu	Trp	His	Thr	Glu. 575	Glu
Phe	Glu	Asp	Gly 580	Arg	Glu	Thr	Gln	Ser 585	Ser	Glu	Ser	Thr	Asn 590	Glu	Phe
Gly	Ile	Phe 595	Asn	Ser	Leu	Trp	Phe 600	Ser	Leu	Gly	Ala	Phe 605	Met	Arg	Gln
Gly	Cys 610	Asp	Ile	Ser	Pro	Arg	Ser	Leu	Ser	Gly	Arg 620	Ile	Val	Gly	Gly
Val 625	Trp	Trp	Phe	Phe	Thr 630	Leu	Ile	Ile	Ile	Ser 635	Ser	Tyr	Thr	Ala	Asn 640
Leu	Ala	Ala	Phe	Leu 645	Thr	Val	Glu	Arg	Met 650	Val	Ser	Pro	Ile	Glu 655	Ser
Ala	Glu	Asp	Leu 660		Lys	Gln	Thr	Glu 665	Ile	Ala	Tyr	Gly	Thr 670	Leu	Asp
Ser	Gly	Ser 675		Lys	Glu	Phe	Phe 680	Arg	Arg	Ser	Lys	Ile 685	Ala	Val	Phe
Asp	Lys 690		Trp	Thr	Tyr	Met 695	Arg	Ser	Ala	Glu	700	Ser	Val	Phe	Val
Arg 705		Thr	Ala	Glu	Gly 710	Val	Ala	Arg	Val	Arc 715		Ser	Lys	Gly	Lys 720
Tyr	Ala	Туг	Leu	1 Leu 7 <u>2</u> 5		Ser	Thr	Met	730	Glu	туг	Ile	e Glu	Gln 735	Arg
Lys	s Pro	су:	74(Met	. Lys	val	Gly 745	Gly	/ Asr	ı Let	ı Asp	750	Lys	Gly
Ту	c Gly	7 Ile 75		a Thr	Pro	Lys	760		Ser	Lev	ı Gly	765	Pro	Val	. Asr
Le	u Ala 770		l Le	u Lys	s Lev	3 Se3	c Glu 5	Glr	ı Gly	y Va	1 Lei 780	Asp C	p Lys	Lev	ı Lys
As:		s Tr	p Tr	р Туз	r Asp 790		s Gly	/ Glu	ı Xaa	a Gl; 79	y Xaa 5	a Gl	y Glu	ı Val	800
Pr	o Ar	g Se	r Al	a Pro 80!		l Ar	g Lys	s Val	1 Met 81	t Gl O	y As	n Se	r Met	Glr 815	n Ası
Ly	s Va	l Se	r Se 82		r Ty	r Al	a Glr	n Cys 825	s Gl; 5	y Hi	s Se	r Va	1 His	s Pro	o Se

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Phe Gln Arg Leu Ser 835

<210> 94

<211> 156

<212> PRT

<213> Homo sapiens

<400> 94

Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys 55

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn 70

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu

Arg His Ala Glu Gly Thr Phe Thr Ser Val Ile Phe Pro Glu Glu Val 105

Ala Ile Val Glu Glu Leu Gly Arg Arg His Ala Asp Gly Ser Phe Ser 115

Asp Glu Met Asn Thr Ile Ser Asp Asn Leu Ala Ala Arg Asp Phe Ile 135

Asn Trp Leu Ile Gln Thr Lys Ile Thr Asp Arg Lys

<210> 95

<211> 303

<212> PRT

<213> Homo sapiens

Met Leu Ser Phe Ile Ser Gly Thr Ala Arg Lys Thr Leu His Phe Glu

Ile Ser Lys Glu Gly Ser Asp Leu Ser Val Val Glu Arg Ala Glu Val

Trp Leu Phe Leu Lys Val Pro Lys Ala Asn Arg Thr Arg Thr Lys Val

Thr Ile Arg Leu Phe Gln Gln Gln Lys His Pro Gln Gly Ser Leu Asp 55

Thr Gly Glu Glu Ala Glu Glu Val Gly Leu Lys Gly Glu Arg Ser Glu

80 • 75 70 65 Leu Leu Ser Glu Lys Val Val Asp Ala Arg Lys Ser Thr Trp His Val Phe Pro Val Ser Ser Ile Gln Arg Leu Leu Asp Gln Gly Lys 105 Ser Ser Leu Asp Val Arg Ile Ala Cys Glu Gln Cys Gln Glu Ser Gly 115 Ala Ser Leu Val Leu Gly Lys Lys Lys Lys Glu Glu Glu Gly Glu Gly Lys Lys Gly Gly Gly Glu Gly Gly Ala Gly Ala Asp Glu 155 Glu Lys Glu Gln Ser His Arg Pro Phe Leu Met Leu Gln Ala Arg Gln 170 Ser Glu Asp His Pro His Arg Arg Arg Arg Gly Leu Glu Cys Asp 185 Gly Lys Val Asn Ile Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys 195 Asp Ile Gly Trp Asn Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala 215 Asn Tyr Cys Glu Gly Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly 235 · 230 Ser Ser Leu Ser Phe His Ser Thr Val Ile Asn His Tyr Arg Met Arg 245 Gly His Ser Pro Phe Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys 265 Leu Arg Pro Met Ser Met Leu Tyr Tyr Asp Asp Gly Gln Asn Ile Ile 275 Lys Lys Asp Ile Gln Asn Met Ile Val Glu Glu Cys Gly Cys Ser 295 <210> 96 <211> 194 <212> PRT <213> Homo sapiens <400> 96 Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu Gly Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr

Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile

****	01/50	.032													
	50					55					60				
Ser 65	Ala	Leu	Arg	Lys	Glu 70	Thr	Cys	Asn	Xaa	Ser 75	Asn	Met ·	Cys	Glu	Lys 80
Asp	Gly	Cys	Phe	Gln 85	Ser	Gly	Phe	Asn	Glu 90	Glu	Thr	Cys	Leu	Val 95	Lys
Ile	Ile	Thr	Gly 100	Leu	Leu	Glu	Phe	Glu 105	Val	Tyr	Leu	Glu	Tyr 110	Leu	Gln
Asn	Arg	Phe	Glu	Ser	Ser	Glu	Glu 120	Gln	Ala	Arg	Ala	Val 125	Gln	Met	Ser
Thr	Lys 130	Val	Leu	Ile	Gln	Phe 135	Leu	Gln	Lys	Lys	Ala 140	Lys	Asn	Leu	Asp
Ala 145		Thr	Thr	Pro	Asp 150	Pro	Thr	Thr	Asn	Ala 155	Ser	Leu	Leu	Thr	Lys 160
Leu	Gln	Ala	Gln	Asn 165	Gln	Trp	Leu	Gln	Asp 170	Met	Thr	Thr	His	Leu 175	Ile
Leu	Arg	Ser	Phe 180	Lys	Glu	Phe	Leu	Gln 185	Ser	Ser	Leu	Arg	Ala 190	Leu	Arg
Gln	Met														
<21 <21	.0> 9 .1> 1 .2> P .3> H	48 PRT	sapi	ens											
<40 Met		97 n Sei	r Phe	Ser		Thr	Cys	Asn	Lys	Ser	Asn	Met	. Cys	Glu 15	Ser
Sei	c Lys	s Glu	ı Ala 20		ı Ala	Glu	. Asn	Asn 25	Leu)	. Asn	Leu	Pro	Lys 30	Met	: Ala
Glu	ı Lys	s Ası 3	o Gly 5	/ Cys	s Phe	Glr	Ser 40	Gly	/ Phe	e Asn	Glu	Glu 45	ı Thr	Cys	. Leu
Va:	l Ly:	-	e Ile	e Thi	c Gly	Leu 55	Leu S	ı Glu	ı Phe	e Glu	val 60	Туз	r Lev	ı Glu	туі
T O	n Gli	n As	n Arc	ı Phe	e Glu	. Sei	Ser	: Glu	ı Glı	ı Glr	n Ala	a Arc	g Ala	a Val	l Glı

80 75 70 65

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn 85

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu 100

Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His

Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala

130 135 140

Leu Arg Gln Met 145

<210> 98

<211> 220

<212> PRT

<213> Homo sapiens

<400> 98

Met Pro Arg Leu Phe Leu Phe His Leu Leu Glu Phe Cys Leu Leu 1 5 10 15

Asn Gln Phe Ser Arg Ala Val Ala Ala Lys Trp Lys Asp Asp Val Ile 20 25 30

Lys Leu Cys Gly Arg Glu Leu Val Arg Ala Gln Ile Ala Ile Cys Gly
35 40 45

Met Ser Thr Trp Ser Lys Arg Ser Leu Ser Gln Glu Asp Ala Pro Gln 50 55 60

Thr Pro Arg Pro Val Ala Ala Gly Asp Phe Ile Gln Thr Val Ser Leu 65 70 75 80

Gly Ile Ser Pro Asp Gly Gly Lys Ala Leu Arg Thr Gly Ser Cys Phe
85 90 95

Thr Arg Glu Phe Leu Gly Ala Leu Ser Lys Leu Val Pro Ser Phe Ile 100 105 110

Asn Lys Asp Thr Glu Thr Ile Ile Ile Met Leu Glu Phe Ile Ala Asn 115 120 125

Leu Pro Pro Glu Leu Lys Ala Ala Leu Ser Glu Arg Gln Pro Ser Leu 130 135 140

Pro Glu Leu Gln Gln Tyr Val Pro Xaa Leu Lys Asp Ser Ser Leu Leu 145 150 155 160

Phe Glu Glu Phe Lys Lys Leu Ile Arg Asn Arg Gln Ser Glu Ala Ala 165 170 175

Asp Ser Asn Pro Ser Glu Leu Lys Tyr Leu Gly Leu Asp Thr His Ser 180 185 190

Gln Lys Lys Arg Arg Pro Tyr Val Ala Leu Phe Glu Lys Cys Cys Leu 195 200 205

Ile Gly Cys Thr Lys Arg Ser Leu Ala Lys Tyr Cys 210 215 220

<210> 99

<211> 87

<212> PRT

<213> Homo sapiens

<400> 99

Met 1	Lys	Leu	Cys	Val 5	Thr	Val	Leu	Ser	Leu 10	Leu	Met	Leu	Val	Ala 15	Ala
Phe	Cys	Ser	Pro 20	Ala	Leu	Ser	Ala	Pro 25	Met	Gly	Ser	Asp	Pro 30	Pro	Thr
Ala	Cys	Cys 35	Phe	Ser	Tyr	Thr	Ala 40	Arg	Lys	Leu	Pro	Arg 45	Asn	Phe	Val
Val	Asp 50	Tyr	Tyr	Glu	Thr	Ser 55	Ser	Leu	Cys	Ser	Gln 60	Pro	Ala	Val	Val
Gly 65	Lys	Gln	Val	Cys	Ala 70	Asp	Pro	Ser	Glu	Ser 75	Trp	Val	Gln	Glu	Tyr 80
Val	Tyr	Asp	Leu	Glu 85	Leu	Asn									
<211 <212)> 10 L> 73 2> PE B> Ho	31 RT	sapie	ens		·									
)> 1(Gly		Ala	Trp 5	Gly	Leu	Gly	Val	Leu 10	Phe	Leu	Met	His	Val 15	Cys
Gly	Thr	Asn	Arg 20	Ile	Pro	Glu	Ser	Gly 25	Gly	Asp	Asn	Ser	Val 30	Phe	Asp
Ile	Phe	Glu 35	Leu	Thr	Gly	Ala	Ala 40	Arg	Lys	Gly	Ser	Gly 45	Arg	Arg	Leu
Val	Lys 50	Gly	Pro	Asp	Pro	Ser 55	Ser	Pro	Ala	Phe	Arg 60	Ile	Glu	Asp	Ala
Asn 65	Leu	Ile	Pro	Pro	Val 70	Pro	Asp	Asp	Lys	Phe 75	Gln	Asp	Leu	Val	Asp 80
Ala	Val	Arg	Ala	Glu 85	Lys	Gly	Phe	Leu	Leu 90	Leu	Ala	Ser	.Leu	Arg 95	Gln
Met	Lys	Lys	Thr 100	Arg	Gly	Thr	Leu	Leu 105	Ala	Leu	Glu	Arg	Lys 110	Asp	His
Ser	Gly	Gln 115	Val	Phe	Ser	Val	Val 120	Ser	Asn	Gly	Lys	Ala 125	Gly	Thr	Leu
Asp	Leu 130	Ser	Leu	Thr	Val	Gln 135	Gly	Lys	Gln	His	Val 140	Val	Ser	Val	Glu
Glu 145	Ala	Leu	Leu	Ala	Thr 150	Gly	Gln	Trp	Lys	Ser 155	Ile	Thr	Leu	Phe	Val 160
Gln	Glu	Asp	Arg	Ala 165	Gln	Leu	Tyr	Ile	Asp 170	Cys	Glu	Lys	Met	Glu 175	Asn
Ala	Glu	Leu	Asp 180	Val	Pro	Ile	Gln	Ser 185	Val	Phe	Thr	Arg	Asp 190	Leu	Ala

Ser	Ile	Ala 195	Arg	Leu	Arg	Ile	Ala 200	Lys	Gly	Gly	Val	Asn 205	Asp	Asn	Phe
Gln	Gly 210	Val	Leu	Gln	Asn	Val 215	Arg	Phe	Val	Phe	Gly 220	Thr	Thr	Pro	Glu
Asp 225	Ile	Leu	Arg	Asn	Lys 230	Gly	Cys	Ser	Ser	Ser 235	Thr	Ser	Val	Leu	Leu 240
Thr	Leu	Asp	Asn	Asn 245	Val	Val	Asn	Gly	Ser 250	Ser	Pro	Ala	Ile	Arg 255	Thr
Asn	Tyr	Ile	Gly 260	His	Lys	Thr	Lys	Asp 265	Leu	Gln	Ala	Ile	Cys 270	Gly	Ile
Ser	Cys	Asp 275	Glu	Leu	Ser	Ser	Met 280	Val	Leu	Glu	Leu	Arg 285	Gly	Leu	Arg
Thr	Ile 290	Val	Thr	Thr	Leu	Gln 295	Asp	Ser	Ile	Arg	Lys 300	Val	Thr	Glu	Glu
Asn 305	Lys	Glu	Leu	Ala	Asn 310	Glu	Leu	Arg	Arg	Pro 315	Pro	Leu	Cys	Tyr	His 320
			•	325			Asn		330					333	
			340					345					350		Ser
Cys	Pro	1le 355		Pro	Cys	Ser	Asn 360	Ala	Thr	Val	Pro	Asp 365	Gly	Glu	Cys
_	370)				375)				380				Pro
385	•				390					395)				Gln 400
				405)				410)				410	
			420)			٠	425	5				430	,	g Phe
		435	5				440					44:)		s Ser
	45	0				45.	5				460	J			n Ser
Pr 46		r Pr	o Gli	n Met	470		у Гуз	s Pr	о Су	s Gl: 47	u Gly 5	y Gl	u Ala	a Aro	g Glu 480
				48	5				49	0				49	
Pr	o Tr	p Se	r Pr 50		p Ası	o Il	e Cy	s Se 50	r Va 5	l Th	r Cy	s Gl	y Gl 51	y G1 0	y Val
Gl	n I.v	s Ar	a Se	r Ar	g Lei	ц Су	s As	n As	n Pr	o Th	r Pr	o Gl	n Ph	e Gl	y Gly

515 520 525 Lys Asp Cys Val Gly Asp Val Thr Glu Asn Gln Ile Cys Asn Lys Gln 535 Asp Cys Pro Ile Asp Gly Cys Leu Ser Asn Pro Cys Phe Ala Gly Val 550 555 Lys Cys Thr Ser Tyr Pro Asp Gly Ser Trp Lys Cys Gly Ala Cys Pro Pro Gly Tyr Ser Gly Asn Gly Ile Gln Cys Thr Asp Val Asp Glu Cys Lys Glu Val Pro Asp Ala Cys Phe Asn His Asn Gly Glu His Arg Cys Glu Asn Thr Asp Pro Gly Tyr Asn Cys Leu Pro Cys Pro Pro Arg Phe Thr Gly Ser Gln Pro Phe Gly Gln Gly Val Glu His Ala Thr Ala Asn Lys Gln Val Cys Lys Pro Arg Asn Pro Cys Thr Asp Gly Thr His Asp 645 . 650 Cys Asn Lys Asn Ala Lys Cys Asn Tyr Leu Gly His Tyr Ser Asp Pro Met Tyr Arg Cys Glu Cys Lys Pro Gly Tyr Ala Gly Asn Gly Ile Ile 680 Cys Gly Glu Asp Thr Asp Leu Asp Gly Trp Pro Asn Glu Asn Leu Val Cys Val Ala Asn Ala Thr Tyr His Cys Lys Lys Asp Asn Cys Pro Asn 710 Leu Pro Gln Asp Pro Ala Pro Cys Pro Arg Ser 725

<210> 101

<211> 555

<212> PRT

<213> Homo sapiens

<400> 101

Met Gly Leu Ala Trp Gly Leu Gly Val Leu Phe Leu Met His Val Cys
1 5 10 15

Gly Thr Asn Arg Ile Pro Glu Ser Gly Gly Asp Asn Ser Val Phe Asp 20 25 30

Ile Phe Glu Leu Thr Gly Ala Ala Arg Lys Gly Ser Gly Arg Arg Leu
35 40 45

Val Lys Gly Pro Asp Pro Ser Ser Pro Ala Phe Arg Ile Glu Asp Ala 50 55 60

Asn Leu Ile Pro Pro Val Pro Asp Asp Lys Phe Gln Asp Leu Val Asp

65					70					75					80
Ala	Val	Arg	Ala	Glu 85	Lys	Gly	Phe	Leu	Leu 90	Leu	Ala	Ser	Leu	Arg 95	Gl'n
Met	Lys	Lys	Thr 100	Arg	Gly	Thr	Leu	Leu 105	Ala	Leu	Glu	Arg	Lys 110	Asp	His
Ser	Gly	Gln 115	Val	Phe	Ser	Val	Val 120	Ser	Asn	Gly	Lys	Ala 125	Gly	Thr	Leu
Asp	Leu 130	Ser	Leu	Thr	Val	Gln 135	Gly	Lys	Gln	His	Val 140	Val	Ser	Val	Glu
Glu 145	Ala	Leu	Leu	Ala	Thr 150	Gly	Gln	Trp	Lys	Ser 155	Ile	Thr	Leu	Phe	Val 160
Gln	Glu	Asp	Arg	Ala 165	Gln	Leu	Tyr	Ile	Asp 170	Cys	Glu	Lys	Met	Glu 175	Asn
			180					185					Asp 190		
		195					200				•	205	Asp		
	210					215					220		Thr		
225					230					235			Val		240
		_		245					250				Ile	255	
	-		260					265					Cys 270		
		275					280.		i			285			
	290					295					300		Thr		
305	-				310					315			Cys		320
				325					330	٠			Asp	335	,
			340					345					Lys 350		
-		355					360		٠.			365	Gly		
_	370					375					380		Trp		
385		GIU	ттЪ	111T	390		⊃∈T	1111	OEL	395		7.571	- + y		400

Gln Arg Gly Arg Ser Cys Asp Ser Leu Asn Asn Arg Cys Glu Gly Ser Ser Val Gln Thr Arg Thr Cys His Ile Gln Glu Cys Asp Lys Arg Phe 425 Lys Gln Asp Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser Cys Ser 440 Val Thr Cys Gly Asp Gly Val Ile Thr Arg Ile Arg Leu Cys Asn Ser 4.55 Pro Ser Pro Gln Met Asn Gly Lys Pro Cys Glu Gly Glu Ala Arg Glu 475 470 Thr Lys Ala Cys Lys Lys Asp Ala Cys Pro Ile Asn Gly Gly Trp Gly 490 Pro Trp Ser Pro Trp Asp Ile Cys Ser Val Thr Cys Gly Gly Val Gln Lys Arg Ser Arg Leu Cys Asn Asn Pro Thr Pro Gln Phe Gly Gly 520 Lys Asp Cys Val Gly Asp Val Thr Glu Asn Gln Ile Cys Asn Lys Gln 535 Asp Cys Pro Ile Gly Glu Pro Arg Ser Pro Gly 550 <210> 102 <211> 546 <212> PRT <213> Homo sapiens <400> 102 Met Gly Leu Ala Trp Gly Leu Gly Val Leu Phe Leu Met His Val Cys Gly Thr Asn Arg Ile Pro Glu Ser Gly Gly Asp Asn Ser Val Phe Asp Ile Phe Glu Leu Thr Gly Ala Ala Arg Lys Gly Ser Gly Arg Arg Leu Val Lys Gly Pro Asp Pro Ser Ser Pro Ala Phe Arg Ile Glu Asp Ala 55 50 Asn Leu Ile Pro Pro Val Pro Asp Asp Lys Phe Gln Asp Leu Val Asp 75 70 Ala Val Arg Ala Glu Lys Gly Phe Leu Leu Leu Ala Ser Leu Arg Gln 90 Met Lys Lys Thr Arg Gly Thr Leu Leu Ala Leu Glu Arg Lys Asp His Ser Gly Gln Val Phe Ser Val Val Ser Asn Gly Lys Ala Gly Thr Leu 120 115

Asp	Leu 130	Ser	Leu	Thr	Vaļ	Gln 135	Gly	Lys	Gln	His	Val 140	Val	Ser	Val	Glu
Glu 145	Ala	Leu	Leu	Ala	Thr 150	Gly	Gln	Trp	Lys	Ser 155	Ile	Thr	Leu	Phe	Val 160
Gln	Glu	Asp	Arg	Ala [.] 165	Gln	Leu	Tyr	Ile	Asp 170	Cys	Glu	Lys	Met	Glu 175	Asn
Ala	Glu	Leu	Asp 180	Val	Pro	Ile	Gln	Ser 185	Val	Phe	Thr	Arg	Asp 190	Leu	Ala
Ser	Ile	Ala 195	Arg	Leu	Arg	Ile	Ala 200	Lys	Gly	Gly	Val	Asn 205	Asp	Asn	Phe
Gln	Gly 210	Val	Leu	Gln	Asn	Val 215	Arg	Phe	Val	Phe	Gly 220	Thr	Thr	Pro	Glu
Asp 225	Ile	Leu	Arg	Asn	Lys 230	Gly	Cys	Ser	Ser	Ser 235	Thr	Ser	Val	Leu	Leu 240
Thr	Leu	Asp	Asn	Asn 245	Val	Val	Asn	Gly	Ser 250	Ser	Pro	Ala	Ile	Arg 255	Thr
Asn	Tyr	Ile	Gly 260	His	Lys	Thr	Lys	Asp 265	Leu	Gln	Ala	Ile	Cys 270	Gly	Ile
Ser	Cys	Asp 275	Glu	Leu	Ser	Ser	Met 280	Val	Leu	Glu	Leu	Arg 285	Gly	Leu	Arg
Thr	Ile 290	Val	Thr	Thr	Leu	Gln 295	Asp	Ser	Ile	Arg	Lys 300	Val	Thr	Glu	Glu
Asn 305	Lys	Glu	Leu	Ala	Asn 310	Glu	Leu	Arg	Arg	Pro 315	Pro	Leu	Cys	Tyr	His 320
Asn	Gly	Val	Gln	Tyr 325	Arg	Asn	Àsn	Glu	Glu 330	Trp	Thr	Val	Asp	Ser 335	Cys
Thr	Glu	Ċуs	His 340	Cys	Gln	Asn	Ser	Val 345	Thr	Ile	Cys	Lys	Lys 350	Val	Ser
Cys	Pro	Ile 355	Met	Pro	Cys	Ser	Asn 360	Ala	Thr	Val	Pro	Asp 365	Gly	Glu	Cys
Cys	Pro 370	Arg	Cys	Trp	Pro	Ser 375	Asp	Ser	Ala	Asp	Asp 380	Gly	Trp	Ser	Pro
Trp 385	Ser	Glu	Trp	Thr	Ser 390	Cys	Ser	Thr	Ser	Cys 395	Gly	Asn	Gly	Ile	Gln 400
Gln	Arg	Gly	Arg	Ser 405	Cys	Asp	Ser	Leu	Asn 410	Asn	Arg	Cys	Glu	Gly 415	Ser
Ser	Val	Gln	Thr 420	Arg	Thr	Cys	His	Ile 425	Gln	Glu	Cys	Asp	Lys 430	Arg	Phe
Lys	Gln	Asp 435	Gly	Gly	Trp	Ser	His 440	Trp	Ser	Pro	Trp	Ser 445	Ser	Cys	Ser

Val Thr Cys Gly Asp Gly Val Ile Thr Arg Ile Arg Leu Cys Asn Ser 455 Pro Ser Pro Gln Met Asn Gly Lys Pro Cys Glu Gly Glu Ala Arg Glu 475 Thr Lys Ala Cys Lys Lys Asp Ala Cys Pro Ser Lys Cys Glu Val Arg Cys Lys Gly Glu His Gly Gln Gln Leu Cys Pro Ala Gly Cys Leu Gly 505 Ile Cys Ser Leu Gln Phe Gln Trp Gly His Arg Ser Arg Lys Val Thr 520 Tyr Leu Gly Glu Thr Asn Arg Arg Gln Ser Pro Ala Gly Ser Ala Thr 535 Ser Phe 545 <210> 103 <211> 459 <212> PRT <213> Homo sapiens <400> 103 Met Gly Leu Ala Trp Gly Leu Gly Val Leu Phe Leu Met His Val Cys Gly Thr Asn Arg Ile Pro Glu Ser Gly Gly Asp Asn Ser Val Phe Asp Ile Phe Glu Leu Thr Gly Ala Ala Arg Lys Gly Ser Gly Arg Arg Leu 45 Val Lys Gly Pro Asp Pro Ser Ser Pro Ala Phe Arg Ile Glu Asp Ala 55 Asn Leu Ile Pro Pro Val Pro Asp Asp Lys Phe Gln Asp Leu Val Asp Ala Val Arg Ala Glu Lys Gly Phe Leu Leu Leu Ala Ser Leu Arg Gln Met Lys Lys Thr Arg Gly Thr Leu Leu Ala Leu Glu Arg Lys Asp His 105 Ser Gly Gln Val Phe Ser Val Val Ser Asn Gly Lys Ala Gly Thr Leu 120 Asp Leu Ser Leu Thr Val Gln Gly Lys Gln His Val Val Ser Val Glu 135 Glu Ala Leu Leu Ala Thr Gly Gln Trp Lys Ser Ile Thr Leu Phe Val 150 Gln Glu Asp Arg Ala Gln Leu Tyr Ile Asp Cys Glu Lys Met Glu Asn 170 165

Ala Glu Leu Asp Val Pro Ile Gln Ser Val Phe Thr Arg Asp Leu Ala 180 185 190

- Ser Ile Ala Arg Leu Arg Ile Ala Lys Gly Gly Val Asn Asp Asn Phe 195 200 205
- Gln Gly Val Leu Gln Asn Val Arg Phe Val Phe Gly Thr Thr Pro Glu 210 215 220
- Asp Ile Leu Arg Asn Lys Gly Cys Ser Ser Ser Thr Ser Val Leu Leu 225 230 235 240
- Thr Leu Asp Asn Asn Val Val Asn Gly Ser Ser Pro Ala Ile Arg Thr 245 250 255
- Asn Tyr Ile Gly His Lys Thr Lys Asp Leu Gln Ala Ile Cys Gly Ile 260 265 270
- Ser Cys Asp Glu Leu Ser Ser Met Val Leu Glu Leu Arg Gly Leu Arg 275 280 285
- Thr Ile Val Thr Thr Leu Gln Asp Ser Ile Arg Lys Val Thr Glu Glu 290 295 300
- Asn Lys Glu Leu Ala Asn Glu Leu Arg Arg Pro Pro Leu Cys Tyr His 305 310 315
- Asn Gly Val Gln Tyr Arg Asn Asn Glu Glu Trp Thr Val Asp Ser Cys 325 330 335 .
- Thr Glu Cys His Cys Gln Asn Ser Val Thr Ile Cys Lys Lys Val Ser 340 345 350
- Cys Pro Ile Met Pro Cys Ser Asn Ala Thr Val Pro Asp Gly Glu Cys 355 360 365
- Cys Pro Arg Cys Trp Pro Ser Asp Ser Ala Asp Asp Gly Trp Ser Pro 370 375 380
- Trp Ser Glu Trp Thr Ser Cys Ser Thr Ser Cys Gly Asn Gly Ile Gln 385 390 395 400
- Gln Arg Gly Arg Ser Cys Asp Ser Leu Asn Asn Arg Cys Glu Gly Ser
- Ser Val Gln Thr Arg Thr Cys His Ile Gln Glu Cys Asp Lys Arg Cys 420 425 430
- Lys His Leu Ser Leu Ser Gly Thr Trp Arg Thr Asp Leu Ser Leu Leu 435
- Ser Ser Pro Arg Ala Ala Pro Gln His Val Tyr 450 455

<210> 104

<211> 363

<212> PRT

<213> Homo sapiens

<400> 104

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Met 1	Ala	Ala	Leu	Met 5	Thr	Pro	Gly	Thr	Gly 10	Ala	Pro	Pro	Ala	Pro 15	GIÀ
Asp	Phe	Ser	Gly 20	Glu	Gly	Ser	Gln	Gly 25	Leu	Pro	Asp	Pro	Ser 30	Pro	Glu
Pro	Lys	Gln 35	Leu	Pro	Glu	Leu	Ile 40	Arg	Met	Lys	Arg	Asp 45	Gly	Gly	Arg
Leu	Ser 50	Glu	Ala	Asp	Ile	Arg 55	Gly	Phe	Val	Ala	Ala 60	Val	Val	Asn	Gly
Ser 65	Ala	Gln	Gly	Ala	Gln 70	Ile	Gly	Ala	Met	Leu 75	Met	Ala	Ile	Arg	Leu 80
Arg	Gly	Met	Asp	Leu 85	Glu	Glu	Thr	Ser	Val 90	Leu	Thr	Gln	Ala	Leu 95	Ala
Gln	Şer	Gly	Gln 100	Gln	Leu	Glu	Trp	Pro 105	Glu	Ala	Trp	Arg	Gln 110	Gln	Leu
Val	Asp	Lys 115	His	Ser	Thr	Gly	Gly 120	Val	Gly	Asp	Lys	Val 125	Ser	Leu	Val
Leu	Ala 130	Pro	Ala	Leu	Ala	Ala 135	Cys	Gly	Cys	Lys	Val 140	Pro	Met	Ile	Ser
Gly 145	Arg	Gly	Leu	Gly	His 150	Thr	Gly	Gly	Thr	Leu 155	Asp	Lys	Leu	Glu	Ser 160
Ile	Pro	Gly	Phe	Asn 165	Val	Ile	Gln	Ser	Pro 170	Glu	Gln	Met	Gln	Val 175	Leu
Leu	Asp	Gln	Ala 180		Cys	Cys	Ile	Val 185	Gly	Gln	Ser	Glu	Gln 190	Leu	Val
Pro	Ala	Asp 195		Ile	Leu	Tyr	Ala 200		Arg	Asp	Val	Thr 205	Ala	Thr	Val
Asp	Ser 210		Pro	Leu	Ile	Thr 215	Ala	Ser	Ile	Leu	Ser 220	Lys	Lys	Leu	Val
Glu 225		Leu	. Ser	Ala	Leu 230	Val	Val	Asp	Val	Lys 235	Phe	Gly	Gly	Ala	Ala 240
Val	. Phe	Pro	Asr	Gln 245	Glu	Gln	Ala	Arg	Glu 250		Ala	Lys	Thr	Leu 255	Val
Gly	Val	. Gly	7 Ala 260		Leu	Gly	Leu	Arg 265	Val	Ala	Ala	Ala	Leu 270	Thr	Ala
Met	: Asp	275		Leu	ı Gly	Aro	280		Gly	/ His	s Ala	Leu 285	Glu S	Val	Glu
Glu	1 Ala 290		ı Lev	ı Cys	s Met	Asp 295		Ala	a Gly	Pro	300		Leu	Arg	Asp
Let 305		L Thi	r Thi	r Lei	1 Gly 310		/ Ala	Lei	ı Lev	Trp 315		ı Ser	: Gly	His	Ala 320
Gl	y Thi	c Gli	n Ala	a Glr	n Gly	/ Ala	a Ala	a Ar	y Val	L Ala	a Ala	a Ala	a Arç	, Ala	Leu

325 330 335

Gln Glu Ala Leu Val Leu Ser Asp Arg Ala Pro Phe Ala Ala Pro Ser 340 345 350

Pro Phe Ala Glu Leu Val Leu Pro Pro Gln Gln 355 360

<210> 105

<211> 442

<212> PRT

<213> Homo sapiens

<400> 105

Met Ala Ala Leu Met Thr Pro Gly Thr Gly Ala Pro Pro Ala Pro Gly
1 5 10 15

Asp Phe Ser Gly Glu Gly Ser Gln Gly Leu Pro Asp Pro Ser Pro Glu 20 25 30

Pro Lys Gln Leu Pro Glu Leu Ile Arg Met Lys Arg Asp Gly Gly Arg
35 40 45

Leu Ser Glu Ala Asp Ile Arg Gly Phe Val Ala Ala Val Val Asn Gly 50 55 60

Ser Ala Gln Gly Ala Gln Ile Gly Ala Met Leu Met Ala Ile Arg Leu 65 70 75 80

Arg Gly Met Asp Leu Glu Glu Thr Ser Val Leu Thr Gln Ala Leu Ala 85 90 95

Gln Ser Gly Gln Gln Leu Glu Trp Pro Glu Ala Trp Arg Gln Gln Leu 100 105 110

Val Asp Lys His Ser Thr Gly Gly Val Gly Asp Lys Val Ser Leu Val 115 120 125

Leu Ala Pro Ala Leu Ala Ala Cys Gly Cys Lys Val Pro Met Ile Ser 130 135 140

Gly Arg Gly Leu Gly His Thr Gly Gly Thr Leu Asp Lys Leu Glu Ser 145 150 155 160

Ile Pro Gly Phe Asn Val Ile Gln Ser Pro Glu Gln Met Gln Val Leu 165 170 175

Leu Asp Gln Ala Gly Cys Cys Ile Val Gly Gln Ser Glu Gln Leu Val 180 185 190

Pro Ala Asp Gly Ile Leu Tyr Ala Ala Arg Asp Val Thr Ala Thr Val 195 200 205

Asp Ser Leu Pro Leu Ile Thr Gly Trp Arg Gly Ser Gln Pro Arg Ala 210 215 220

Arg Val Ala Ala Ala Leu Thr Ala Met Asp Lys Pro Leu Gly Arg Cys 235 230 235

Val Gly His Ala Leu Glu Val Glu Glu Ala Leu Leu Cys Met Asp Gly

PCT/IL00/00766

245 250 255

Ala Gly Pro Pro Asp Leu Arg Asp Leu Val Thr Thr Leu Gly Gly Ala 260 265 270

Leu Leu Trp Leu Ser Gly His Ala Gly Thr Gln Ala Gln Gly Ala Ala 275 280 285

Arg Val Ala Ala Ala Leu Asp Asp Gly Ser Ala Leu Gly Arg Phe Glu 290 295 300

Arg Met Leu Ala Ala Gln Gly Val Asp Pro Gly Leu Ala Arg Ala Leu 305 310 315 320

Cys Ser Gly Ser Pro Ala Glu Arg Arg Gln Leu Leu Pro Arg Ala Arg 325 330 335

Glu Gln Glu Leu Leu Ala Pro Ala Asp Gly Thr Val Glu Leu Val 340 345 350

Arg Ala Leu Pro Leu Ala Leu Val Leu His Glu Leu Gly Ala Gly Arg 355 360 365

Ser Arg Ala Gly Glu Pro Leu Arg Leu Gly Val Gly Ala Glu Leu Leu 370 375 380

Val Asp Val Gly Gln Arg Leu Arg Arg Gly Thr Pro Trp Leu Arg Val 385 390 395 400

His Arg Asp Gly Pro Ala Leu Ser Gly Pro Gln Ser Arg Ala Leu Gln
405 410 415

Glu Ala Leu Val Leu Ser Asp Arg Ala Pro Phe Ala Ala Pro Ser Pro 420 425 430

Phe Ala Glu Leu Val Leu Pro Pro Gln Gln

<210> 106

<211> 323

<212> PRT

<213> Homo sapiens

<400> 106

Met Ala Ala Leu Met Thr Pro Gly Thr Gly Ala Pro Pro Ala Pro Gly
1 5 .10 15

Asp Phe Ser Gly Glu Gly Ser Gln Gly Leu Pro Asp Pro Ser Pro Glu 20 25 30

Pro Lys Gln Leu Pro Glu Leu Ile Arg Met Lys Arg Asp Gly Gly Arg
35 40 45

Leu Ser Glu Ala Asp Ile Arg Gly Phe Val Ala Ala Val Val Asn Gly 50 55 60

Ser Ala Gln Gly Ala Gln Ile Gly Ala Met Leu Met Ala Ile Arg Leu 65 70 75 80

Arg Gly Met Asp Leu Glu Glu Thr Ser Val Leu Thr Gln Ala Leu Ala

		85					90					95	
	 	~ .	_	0.1	m	D	C)	71.	m~~	7 ~ ~	Cln	Cln	

Gln Ser Gly Gln Gln Leu Glu Trp Pro Glu Ala Trp Arg Gln Gln Leu 100 105 110

Val Asp Lys His Ser Thr Gly Gly Val Gly Asp Lys Val Ser Leu Val 115

Leu Ala Pro Ala Leu Ala Ala Cys Gly Cys Lys Val Pro Met Ile Ser 130 135 140

Gly Arg Gly Leu Gly His Thr Gly Gly Thr Leu Asp Lys Leu Glu Ser 145 150 155 160

Ile Pro Gly Phe Asn Val Ile Gln Ser Pro Glu Gln Met Gln Val Leu 165 170 175

Leu Asp Gln Ala Gly Cys Cys Ile Val Gly Gln Ser Glu Gln Leu Val 180 185 190

Pro Ala Asp Gly Ile Leu Tyr Ala Ala Arg Asp Val Thr Ala Thr Val 195 200 205

Asp Ser Leu Pro Leu Ile Thr Gly Trp Arg Gly Ser Gln Pro Arg Ala 210 215 220

Arg Val Ala Ala Ala Leu Thr Ala Met Asp Lys Pro Leu Gly Arg Cys 225 230 235 240

Val Gly His Ala Leu Glu Val Glu Glu Ala Leu Leu Cys Met Asp Gly 245 250 255

Ala Gly Pro Pro Asp Leu Arg Asp Leu Val Thr Thr Leu Gly Gly Ala

Leu Leu Trp Leu Ser Gly His Ala Gly Thr Gln Ala Gln Gly Ala Ala

Arg Val Ala Ala Ala Arg Ala Leu Gln Glu Ala Leu Val Leu Ser Asp 290 295 300

Arg Ala Pro Phe Ala Ala Pro Ser Pro Phe Ala Glu Leu Val Leu Pro 305 310 315 320

Pro Gln Gln

<210> 107

<211> 481

<212> PRT

<213> Homo sapiens

<400> 107

Met Ala Ser Arg Leu Thr Leu Leu Thr Leu Leu Leu Leu Leu Leu Ala

Gly Asp Arg Ala Ser Ser Asn Pro Asn Ala Thr Ser Ser Val Ile Ser

Lys Met Leu Phe Val Glu Pro Ile Leu Glu Val Ser Ser Leu Pro Thr

		35					40					45			
Thr	Asn 50	Ser	Thr	Thr	Asn	Ser 55	Ala	Thr	Lys	Ile	Thr 60	Ala	Asn	Thr	Thr
Asp 65	Glu	Pro	Thr	Thr	Gln 70	Pro	Thr	Thr	Glu	Pro 75	Thr	Thr	Gln	Pro	Thr 80
Ile	Gln	Pro	Thr	Gln 85	Pro	Thr	Thr	Gln	Leu 90	Pro	Thr	Asp	Ser	Pro 95	Thr
Gln	Pro	Thr	Thr 100	Gly	Ser	Phe	Cys	Pro 105	Gly	Pro	Val	Thr	Leu 110	Cys	Ser
Asp	Leu	Glu 115	Ser	His	Ser	Thr	Glu 120	Ala	Val	Leu	Gly	Asp 125	Ala	Leu	Val
Asp	Phe 130	Ser	Leu	Lys	Leu	Tyr 135	His	Ala	Phe	Ser	Ala 140	Met	Lys	Lys	Val
Glu 145	Thr	Asn	Met	Ala	Phe 150	Ser	Pro	Phe	Ser	Ile 155	Ala	Ser	Leu	Leu	Thr 160
Gln	Val	Leu	Leu	Gly 165	Ala	Gly	Glu	Asn	Thr 170	Lys	Thr	Asn	Leu	Glu 175	Ser
Ile	Leu	Ser	Туг 180		. Lys	Asp	Phe	Thr 185	Cys	Val	His	Gln	Ala 190	Leu	Lys
Gly	Phe	Thr 195	Thr	Lys	Gly	Val	Thr 200	Ser	Val	Ser	Gln	Ile 205	Phe	His	Ser
Pro	Asp 210	Leu	Ala	Ile	Arg	Asp 215		Phe	Val	Asn	Ala 220	Ser	Arg	Thr	Leu
Tyr 225		Ser	Ser	Pro	Arg 230		Leu	Ser	Asn	Asn 235	Ser	Asp	Ala	Asn	Leu 240
			Asn	245					250					255	
Arg	Leu	Leu	260		Leu	Pro	Ser	Asp 265	Thr	Arg	Leu	Val	Leu 270	Leu	Asn
		275					280					285			
	290)	Glu			295					300)			
Met 305		Asr	n Ser	. Lys	310		r Pro	Val	Ala	315	Ph∈	e Ile	Asp	Gln	Thr 320
Let	Lys	s Alá	a Lys	325		y Glr	ı Lev	ı Glr	330	ı Ser	His	s Asr	l Leu	335	Leu
Val	. Ile	e Lei	u Va. 340		Glr	n Ası	n Lei	1 Lys 345	s His	s Arg	g Let	ı Glu	350	Met	Glu
Glr	n Ala	a Let 35	u Sei 5	r Pro	o Sei	r Val	1 Phe 360	e Lys	s Ala	a Ile	e Met	365	Lys	: Leu	Glu

Met Ser Lys Phe Gln Pro Thr Leu Leu Thr Leu Pro Arg Ile Lys Val Thr Thr Ser Gln Asp Met Leu Ser Ile Met Glu Lys Leu Glu Phe Phe 390 Asp Phe Ser Tyr Asp Leu Asn Leu Cys Gly Leu Thr Glu Asp Pro Asp 410 405 Leu Gln Val Ser Ala Met Gln His Gln Thr Val Leu Glu Leu Thr Glu 425 Thr Gly Val Glu Ala Ala Ala Ser Ala Ile Ser Val Ala Arg Thr 435 Leu Leu Val Phe Glu Val Gln Gln Pro Phe Leu Phe Val Leu Trp Asp 460 455 Gln Gln His Lys Phe Pro Val Phe Met Gly Arg Val Tyr Asp Pro Arg 475 470 Ala <210> 108 <211> 116 <212> PRT <213> Homo sapiens <400> 108 Met Met Asp Glu Glu Val Glu Val Ser Leu Pro Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly Met Ser Gln Thr 40 ; Asp Leu Ser Leu Ser Lys Val Val His Lys Ser Phe Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala Ile Met Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp His Pro Phe Leu Phe Phe Ile Gln His Ser Lys Thr Asn Gly Ile Leu Phe Cys Gly Arg 105 100 Phe Ser Ser Pro 115 <210> 109 <211> 319

<212> PRT

<213> Homo sapiens

	> 10 Asp		Leu	Ala 5	Glu	Ala	Asn	Gly	Thr 10	Phe	Ala	Leu	Asn	Leu 15	Leu
Lys	Thr	Leu	Gly 20	Lys	Asp	Asn	Ser	Lys 25	Asn	Val	Phe	Phe	Ser 30	Pro	Met
Ser	Met	Ser 35	Cys	Ala	Leu	Ala	Met 40	Val	Tyr	Met	Gly	Ala 45	Lys	Gly	Asn
Thr	Ala 50	Ala	Gln	Met	Ala	Gln 55	Ile	Leu	Ser	Phe	Asn 60	Lys	Ser	Gly	Gly
Gly 65	Gly	Asp	Ile	His	Gln 70	Gly	Phe	Gln	Ser	Leu 75	Leu	Thr	Glu	Val	Asn 80
Lys	Thr	Gly	Thr	Gln 85	Tyr	Leu	Leu	Arg	Val 90	Ala	Asn	Arg	Leu	Phe 95	Gly
Glu	Lys	Ser	Cys 100	Asp	Phe	Leu	Ser	Ser 105	Phe	Arg	Asp	Ser	Cys 110	Gln	Lys
Phe	Tyr	Gln 115	Ala	Glu	Met	Glu	Glu 120	Leu	Asp	Phe	Ile	Ser 125	Ala	Val	Glu
Lys	Ser 130	Arg	Lys	His	Ile	Asn 135	Thr	Trp	Val	Ala	Glu 140	Lys	Thr	Glu	Gly
Lys 145	Ile	Ala	Glu	Leu	Leu 150	Ser	Pro	Gly	Ser	Val 155	Asp	Pro	Leu	Thr	Arg 160
Leu	Val	Leu	Val	Asn 165	Ala	Val	Tyr	Phe	Arg 170	Gly	Asn	Trp	Asp	Glu 175	Gln
Phe	Asp	Lys	Glu 180	Asn	Thr	Glu	Glu	Arg 185	Leu	Phe	Lys	Val	Ser 190	Lys	Asn
Glu	Glu	Lys 195		Val	Gln	Met	Met 200		Lys	Gln	Ser	Thr 205	Phe	Lys	Lys
Thr	Tyr 210		Gly	Glu	Ile	Phe 215		Gln	Ile	Leu	Val 220		Pro	Tyr	Val
Gly 225	Lys	Glu	Leu	Asn	Met 230		Ile	Met	Leu	Pro 235		Glu	Thr	Thr	Asp 240
Leu	Arg	Thr	Val	Glu 245		Glu	. Leu	Thr	Tyr 250		Lys	Phe	Val	Glu 255	Trp
Thr	Arg	Leu	Asp 260		Met	Asp	Glu	Glu 265		. Val	Glu	. Glu	Gly 270		Glu
Ala	Ala	Ala 275		Thr	Ala	Ala	1le 280		. Met	: Met	Arg	Cys 285	Ala	Arg	Phe
Val	Pro 290		, Phe	Cys	Ala	Asp 295		Pro	Phe	e Lev	Phe 300		lle	Gln	His
Ser		Thr	Asn	Gly	/ Ile		. Phe	e Cys	Gly	/ Arc	g Phe	Ser	Ser	Pro	

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<210> 110 . <211> 188 <212> PRT

<213> Homo sapiens

<400> 110

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu 10

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly

Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn

Lys Thr Gly Thr Gln Tyr Leu Leu Arg Glu Ser Tyr Asp Met Glu Ser

Val Leu Arg Asn Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala 105

Asp Phe Ser Gly Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Val 120

His Lys Ser Phe Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala 130

Ala Thr Ala Ala Ile Met Met Met Arg Cys Ala Arg Phe Val Pro Arg 155 150

Phe Cys Ala Asp His Pro Phe Leu Phe Phe Ile Gln His Ser Lys Thr 170

Asn Gly Ile Leu Phe Cys Gly Arg Phe Ser Ser Pro 185 180

<210> 111

<211> 60

<212> PRT

<213> Homo sapiens

<400> 111

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn 40

Thr Ala Ala Gln Met Ala Gln Arg Phe Gln Lys Val

50

55

60

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(210) (211)																	
(212)	> PR	T	saj	pier	าร												
<400 Met 1	> 11 His	.2 Lys	: Т	hr <i>l</i>	Ala 5	Ser	Gln	Arg	Leu	Phe 10	Pro	Gly	Pro	Ser	Tyr 15	Gln	
Asn	Ile	Lys	s S	er :	Ile	Met	Glu	Asp	Ser 25	Thr	Ile	Leu	Ser	Asp 30	Trp	Thr	
Asn	Ser	Asr 35		ys	Gln	Lys	Met	Lys 40	Tyr	Asp	Phe	Ser	Cys 45	Glu	Leu	Tyr	
Arg	Met 50	Se	r I	hr.	Tyr	Ser	Thr 55	Phe	Pro	Ala	Gly	Val 60	Pro	Val	Ser	Glu	1
Arg 65	Ser	Le	u F	Ala	Arg	Ala 70	Gly	Phe	Tyr	Tyr	Thr 75	Gly	Val	Asn	Asp	Lys 80))
Val	Lys	Су	s H	?he	Cýs 85	Cys	Gly	Leu	Met	Leu 90	Asp	Asn	Trp	Lys	Leu 95	Gly	7
Asp	Ser	Pr		Ile 100	Gln	Lys	His	Lys	Gln 105	Leu	Tyr	Pro	Ser	Cys 110	Ser	Phe	Э
Ile	Glr	n As 11		Leu	Val	Ser	Ala	Ser 120	Leu	Gly	/ Ser	Thr	Ser 125	Lys	Asn	Th:	r
Ser	Pro		et	Arg	Asn	Ser	Phe 135	Ala	a His	s Sei	Leu	Ser 140	Pro	Thr	Leu	Gl	u
His 145		r Se	er	Leu	Phe	Ser 150	: Gly	, Sei	с Туз	c Sei	r Ser 155	Leu	Ser	Pro	Asr	16	0
					165	Ó				17	U	ser					
Tyr	c Se	r T	yr	Ala 180		: Se	r Th	c Gl	u Gl	u Al 5	a Ar	g Phe	. Leu	190	Ty:	c Hi	.s
Met	t Tr		ro 95	Leu	Thi	r Ph	e Le	u Se 20	r Pr O	o Se	r Gl	u Lev	205	Aro	g Ala	a Gl	ГÀ
	21	.0					21	5				a Cys 220	,				
G1 22		ıs I	eu	Sei	c As	n Tr 23	p G1 0	u Pr	o Ly	s As	sp As 23	n Ala 5	a Me	t Se	r Gl	u H: 2	is 40
Le	u Ai	rg H	lis	Phe	e Pr 24	o As 5	n Cy	s Pi	o Ph	ne Le 25	eu G1 50	u As	n Se	r Le	u Gl 25	u T	hr
·Le	eu A	rg I	Phe	Se.		e Se	er As	n Le	eu Se 20	er Me	et Gl	n Th	r Hi	s Al 27	a Al	a A	rg
Me	et A	rg '	Thr	Ph	e Me	t Ty	r Ti	p P	ro S	er S	er Va	al Pr	o Va	1 G1	n Pi	-o G	lu

285 280 275 Gln Leu Ala Ser Ala Gly Phe Tyr Tyr Val Gly Lys Lys Leu Asn Leu 295 Leu Ile 305 <210> 113 <211> 359 <212> PRT <213> Homo sapiens <400> 113 Met His Ser Ser Met Lys Thr Ser Leu Phe Phe His Ile Val Met Gln Leu Gly Phe Ser Ala Leu Ser Phe Phe Tyr Pro Phe Phe Asn Ser Ser 25 Tyr Tyr Val Gln Met Ile Ile Leu Ser Arg Phe Gly Cys Pro Asp Gln Asn Gly Asp Arg Val Glu Arg Cys Asp Ser Lys Ala Leu Asp Arg Val Ile Xaa Leu Pro Phe Ser Pro Pro Pro Arg Ser Pro Pro Asp Arg Gly 70 Glu His Met Ser Ala Pro Ala Ala Lys Val Ser Lys Lys Glu Leu Asn Ser Asn His Asp Gly Ala Asp Glu Thr Ser Glu Lys Glu Gln Glu Ala Ile Glu His Ile Asp Glu Val Gln Asn Glu Ile Asp Arg Leu Asn 120 115 Glu Gln Ala Ser Glu Glu Ile Leu Lys Vall Glu Gln Lys Tyr Asn Lys 135 130 Leu Arg Gln Pro Phe Phe Gln Lys Arg Ser Glu Leu Ile Ala Lys Ile 155 150 Pro Asn Phe Trp Val Thr Thr Phe Val Asn His Pro Gln Val Ser Ala 170 165 Leu Leu Gly Glu Glu Asp Glu Glu Ala Leu His Tyr Leu Thr Arg Val 185 180 Glu Val Thr Glu Phe Glu Asp Ile Lys Ser Gly Tyr Arg Ile Asp Phe 200 Tyr Phe Asp Glu Asn Pro Tyr Phe Glu Asn Lys Val Leu Ser Lys Glu 215 210 Phe His Leu Asn Glu Ser Gly Asp Pro Ser Ser Lys Ser Thr Glu Ile 235

230

Lys Trp Lys Ser Gly Lys Asp Leu Thr Lys Arg Ser Ser Gln Thr Gln

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250 255 245 Asn Lys Ala Ser Arg Lys Arg Gln His Glu Glu Pro Glu Ser Phe Phe Thr Trp Phe Thr Asp His Ser Asp Ala Gly Ala Asp Glu Leu Gly Glu 280 Val Ile Lys Asp Asp Ile Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Val 295 Pro Asp Met Asp Asp Glu Glu Glu Glu Glu Glu Glu Asp Asp Asp 310 315 Asp Glu Glu Glu Gly Leu Glu Asp Ile Asp Glu Glu Gly Asp Glu 330 325 Asp Glu Gly Glu Glu Asp Glu Asp Asp Asp Glu Gly Glu Gly Glu 345 Glu Asp Glu Gly Glu Asp Asp 355 <210> 114 <211> 261 <212> PRT <213> Homo sapiens <400> 114 Met Ser Ala Pro Ala Ala Lys Val Ser Lys Lys Glu Leu Asn Ser Asn His Asp Gly Ala Asp Glu Thr Ser Glu Lys Glu Gln Gln Glu Ala Ile Glu His Ile Asp Glu Val Gln Asn Glu Ile Asp Arg Leu Asn Glu Gln Ala Ser Glu Glu Ile Leu Lys Val Glu Gln Lys Tyr Asn Lys Leu Arg Gln Pro Phe Phe Gln Lys Arg Ser Glu Leu Ile Ala Lys Ile Pro Asn Phe Trp Val Thr Thr Phe Val Asn His Pro Gln Val Ser Ala Leu Leu 85 Gly Glu Glu Asp Glu Glu Ala Leu His Tyr Leu Thr Arg Val Glu Val 105 Thr Glu Phe Glu Asp Ile Lys Ser Gly Tyr Arg Ile Asp Phe Tyr Phe 120 Asp Glu Asn Pro Tyr Phe Glu Asn Lys Val Leu Ser Lys Glu Phe His 135 Leu Asn Glu Ser Gly Asp Pro Ser Ser Lys Ser Thr Glu Ile Lys Trp

150

Lys Ser Gly Lys Asp Leu Thr Lys Arg Ser Ser Gln Thr Gln Asn Lys

165 170 175

Ala Ser Arg Lys Arg Gln His Glu Glu Pro Glu Ser Phe Phe Thr Trp
180 185 190

Phe Thr Asp His Ser Asp Ala Gly Ala Asp Glu Leu Gly Glu Val Ile 195 200 205

Lys Asp Asp Ile Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Val Pro Asp 210 215 220

Met Asp Asp Glu Glu Gly Glu Gly Glu Glu Asp Asp Asp Asp Glu 225 235 235 240

Glu Glu Glu Gly Leu Glu Asp Ile Asp Glu Glu Gly Asp Gly Gly 245 250 255

Gly Gly Lys Gly Pro 260

<210> 115

<211> 260

<212> PRT

<213> Homo sapiens

<400> 115

Met Leu Ile Ala Ala Gly Pro Ala Arg Thr Gly Val Gly Pro Ala Arg
1 5 10 15

Ile Lys Gly Ala Gln Ala Gly Trp Ala Phe His Arg Pro Ser Ala Leu 20. 25 30

Cys Ser Arg Gly Ala Gly Gln Ala Xaa Ala Ser Glu Leu Ala Ser Arg 35 40 45

His Arg Gly Gly Ala Ala Ala Val Arg Thr Arg Gln Ala Asn Pro Thr 50 55 60

Gln Lys Ser Pro Pro Pro Asp Ser Gln Val Ala Ala Ala Ser Leu Ala 65 70 75 80

His Ala Glu Ser Gly Gly Ala Gly Ser Pro Leu Arg Pro Ala Ser Ala 85 90 95

Leu Ser Ser Ser Pro Phe Pro Phe Phe Ser Leu Ser Ser Pro Leu Ser 100 105 110

Leu Pro Ala Phe Ala Gln Pro Arg Ala Met Ser Asp Ala Ser Leu Arg 115 120 125

Ser Thr Ser Thr Met Glu Arg Leu Val Ala Arg Gly Thr Phe Pro Val 130 135 140

Leu Val Arg Thr Ser Ala Cys Arg Ser Leu Phe Gly Pro Val Asp His 145 150 155 160

Glu Glu Leu Ser Arg Glu Leu Gln Ala Arg Leu Ala Glu Leu Asn Ala 165 170 175

Glu Asp Gln Asn Arg Trp Asp Tyr Asp Phe Gln Gln Asp Met Pro Leu

PCT/1L00/00766

180 185 190

Arg Gly Pro Gly Arg Leu Gln Trp Thr Glu Val Asp Ser Asp Ser Val 195 200 205

Pro Ala Phe Tyr Arg Glu Thr Val Gln Ile Phe Phe Ala Lys Arg Lys 210 215 220

Arg Ser Ala Pro Glu Lys Ser Ser Gly Asp Val Pro Ala Pro Cys Pro 225 230 235 240

Ser Pro Ser Ala Ala Pro Gly Val Gly Ser Val Glu Gln Thr Pro Arg 245 250 255

Lys Arg Leu Arg 260

<210> 116

<211> 582

<212> PRT

<213> Homo sapiens

<400> 116

Met Met Thr Leu Arg His Leu Pro Phe Ile Leu Leu Leu Ile Leu Ser 1 15

Gly Glu Leu Tyr Ala Glu Glu Lys Gln Cys Asp Phe Pro Thr Val Glu 20 25 30

Asn Gly Arg Ile Ala Gln Tyr Tyr Tyr Thr Phe Lys Ser Phe Tyr Phe
35 40 45

Pro Met Ser Val Asp Lys Lys Leu Ser Phe Phe Cys Leu Ala Gly Tyr 50 55 60

Ala Thr Glu Ser Gly Lys Gln Glu Glu Gln Ile Arg Cys Thr Ala Glu 65 70 75 80

Gly Trp Ser Pro Asn Pro Arg Cys Tyr Lys Lys Cys Leu Lys Pro Asp 85 90 95

Leu Arg Asn Gly Tyr Val Ser Asn Asp Lys Val Leu Tyr Lys Leu Gln 100 105 110

Glu Arg Met Ser Tyr Gly Cys Ser Ser Gly Tyr Lys Thr Thr Gly Gly
115 120 125

Lys Asp Glu Glu Val Val His Cys Leu Ser Ala Gly Trp Ser Ser Gln 130 135 140

Pro Ser Cys Arg Lys Glu Gln Glu Thr Cys Leu Ala Pro Glu Leu Glu 145 150 155 160

His Gly Asn Tyr Ser Thr Thr Gln Arg Thr Phe Lys Val Lys Asp Ile 165 170 175

Val Ala Tyr Thr Cys Thr Ala Gly Tyr Tyr Thr Thr Thr Gly Lys Gln 180 185 190

Thr Gly Glu Ala Glu Cys Gln Ala Asn Gly Trp Ser Leu Thr Pro Gln

		195						200						205			
Cys	Asn 210	Lys	Leu	Ме	et C	:ys	Ser 215	Ser	Leu	Ar	:g]	Leu	Ile 220	Glu	Asn	Gly	Tyr
Phe 225	His	Pro	Val	۲,	ys (Gln 230	Thr	Tyr	Glu	G)	Lu (Gly 235	Asp	Val	Val	Gln	Phe 240
Phe	Суѕ	His	Glu	As 24	sn 1	Tyr	Tyr	Leu	Ser	G! 25	ly 50	Ser	Asp	Leu	Ile	Gln 255	Cys
Tyr	Asn	Phe	Gl ₃ 260	7 T:	rp '	ſyr	Pro	Glu	Ser 265	P	ro	Ile	Cys	Glu	Gly 270	Arg	Arg
Asn	Arg	Cys 275) P:	ro	Pro	Pro	Val 280	Pro	L	eu	Asn	Ser	Lys 285	Ile	Gln	Pro
His	Ser 290		Thi	c T	yr .	Arg	His 295	Gly	Glu	Α	rg	Val	His 300	Ile	Glu	Cys	Glu
Leu 305	Asn	Ph∈	va.	l I	le	Gln 310	Gly	Ser	Glu	ı G	lu	Leu 315	Leu	Cys	Glu	Asn	Gly 320
Lys	Trp	Thi	Gl	u P 3	ro 125	Pro	Lys	Cys	Ile	e G 3	1u 30	Glu	Lys	Glu	Lys	Val 335	Ala
Cys	Glu	ı Glı	n Pr 34	0 P	ro	Ser	Val	Glu	Asr 345	n G	ly	Val	Ala	His	Pro 350	His	Ser
Glu	Ile	Ty:		r S	Ser	Gly	Asp	Lys 360	Va.	1 1	hr	Tyr	Arg	Cys 365	Gly	/ Gly	Gly
Tyr	Se:		u Ar	g G	Sly	Ser	Ser 375	Thr	· Il	е 7	hr	Cys	Asn 380	Arg	Gly	y Arg	Trp
Th:		u Pr	o Pr	·o (Glu	Cys 390	Val	. Glu	ı As	n I	Ile	Glu 395	Asn	Cys	. Ly:	s Pro	Pro 400
Pro	As	p Il	e Al	a l	Asn 405	Gly	. Val	. Val	. Va	1 1	Asp 410	GJ?	/ Let	ı Lev	ı Al	a Se:	r Tyr
Th	c Th	r Gl		er :	Ser	Val	. Glu	тул	42	g (5	Cys	Asr	n Glu	і Ту	r Ty 43	r Le	u Leu
Ly	s Gl	у Se 43		lu	Tḥr	Ser	Ar	g Cy:	s G1 0	u	Gln	Gl	y Ala	a.Trj 44	p Se 5	r Se	r Pro
Pr	o Va 45		ıs L	eu	Glu	Pro	Cy:	s Th	r Il	.e	Asp	va.	1 As ₁	p Hi O	s Me	t As	n Arg
As 46		n II	Le G	ln	Leu	Ly:	s Tr	p Ly	s Ty	r	Glu	1 Gl 47	y Ly 5	s Il	e Le	u Hi	s Gly 480
As	p Le	eu I	le A	sp	Phe 485	va S	l Cy	s Ly	s G	ln	G13	у Ту С	r As	n Le	u Se	er Pr 49	o Ser
Il	e Pi	co L	eu S	er 00	Glu	ıIl	e Se	r Al	a G.	ln 05	Су	s As	n Ar	g Gl	y As 51	sp Va 10	ıl Arg
Ţ	r P:		et (ys	Ile	e Ar	g Ly	's Gl 52	.u S 20	er	Ly	s Gl	y M∈	t Cy 52	/s Al 25	la S€	er Pro

Pro Val Ile Arg Asn Gly Asp Ile Val Ser Ser Ala Ala Arg Thr Tyr 530 540

Glu Asn Gly Ser Ser Val Glu Tyr Arg Cys Phe Asp Asn His Phe Leu 545 550 555 555

Gln Gly Ser Gln Asn Val Tyr Cys Val Asp Gly Val Trp Thr Thr Pro 565 570 575

Pro Ser Cys Leu Glu Pro 580

<210> 117

<211> 576

<212> PRT

<213> Homo sapiens

<400> 117

Met Pro Trp Gly Arg Arg Pro Thr Trp Leu Leu Leu Ala Phe Leu Leu 1 5 15

Val Phe Leu Lys Ile Ser Ile Leu Ser Val Thr Ala Trp Gln Thr Gly
20 25 30

Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys
40
45

Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser

Arg Ile Trp Ala Ile Pro Ser Val Ile Arg Val Asn Lys Arg Thr Gly
65 70 75 80

Gln Asn Arg Val Arg Leu Gln Gly Ser Met Leu Lys Pro Ser Ser Leu 85 90 95

Val Val Val His Pro Leu Ala Lys Pro Gly Ala Asp Pro Cys Leu Tyr 100 105 110

Arg Asn Gly Gly Cys Glu His Ile Cys Gln Glu Ser Leu Gly Thr Ala

Arg Cys Leu Cys Arg Glu Gly Phe Val Lys Ala Trp Asp Gly Lys Met 130 135 140

Cys Leu Pro Gln Asp Tyr Pro Ile Leu Ser Gly Glu Asn Ala Asp Leu 145 150 155 . 160

Ser Lys Glu Val Thr Ser Leu Ser Asn Ser Thr Gln Ala Glu Val Pro

Asp Asp Asp Gly Thr Glu Ser Ser Thr Leu Val Ala Glu Ile Met Val 180 185 190

Ser Gly Met Asn Tyr Glu Asp Asp Cys Gly Pro Gly Gly Cys Gly Ser

His Ala Arg Cys Val Ser Asp Gly Glu Thr Ala Glu Cys Gln Cys Leu 210 215 220

Lys 225	Gly	Phe	Ala	Arg	Asp 230	Gly	Asn	Leu	Cys	Ser 235	Asp	Ile	Asp	Glu	Cys 240
Val	Leu	Ala	Arg	Ser 245	Asp	Cys	Pro	Ser	Thr 250	Ser	Ser	Arg	Cys	Ile 255	Asn
Thr	Glu	Gly	Gly 260	Tyr	Val	Cys	Arg	Cys 265	Ser	Glu	Gly	Tyr	Glu 270	Gly	Asp
Gly	Ile	Ser 275	Cys	Phe	Asp	Ile	Asp 280	Glu	Cys	Gln	Arg	Gly 285	Ala	His	Asn
Cys	Ala 290	Glu	Asn	Ala	Ala	Cys 295	Thr	Asn	Thr	Glu	Gly 300	Gly	Tyr	Asn	Cys
Thr 305	Cys	Ala	Gly	Arg	Pro 310	Ser	Ser	Prò	Gly	Leu 315	Ser	Cys	Pro	Asp	Ser 320
Thr	Ala	Pro	Ser	Leu 325	Leu	Gly	Glu	Asp	Gly 330	His	His	Leu	Asp	Arg 335	Asn
Ser	Tyr	Pro	Gly 340	Cys	Pro	Ser	Ser	Tyr 345	Asp	Gly	Tyr	Cys	Leu 350	Asn	Gly
Gly	Val	Cys 355	Met	His	Ile	Glu	Ser 360	Leu	Asp	Ser	Tyr	Thr 365	Cys	Asn	Cys
Val	Ile 370		Туг	Ser	Gly	Asp 375		Cys	Gln	Thr	Arg 380	Asp	Leu	Arg	Trp
Trp 385		Leu	Arg	His	Ala 390		Tyr	Gly	Gln	Lys 395	His	Asp	Ile	Met	Val 400
Val	Ala	Val	Cys	Met 405		Ala	Leu	Val	Leu 410	Leu	Leu	Leu	Leu	Gly 415	Met
Trp	Gly	Thr	Tyr 420		Tyr	Arg	Thr	Arg 425	Lys	Gln	Leu	Ser	Asn 430	Pro	Pro
Lys	a Asn	Pro 435		Asp	Glu	Pro	Ser 440	Gly	Ser	Val	Ser	Ser 445	Ser	Gly	Pro
Asp	Ser 450		Ser	Gly	Ala	Ala 455		. Ala	Ser	Cys	Pro 460	Gln	Pro	Trp	Phe
Val 465		Let	ı Glu	Lys	470		Asp	Pro	Lys	475	Gly	Ser	Leu	Pro	Ala 480
Āsī	Gly	/ Thi	c Asn	Gl ₃ 485		ı Val	. Val	. Asp	Ala 490	Gly	Leu	Ser	Pro	Ser 495	Leu
Gli	n Lei	ı Gl	y Ser 500		L His	s Lev	ı Thi	505	Trp	Arg	g Glr	Lys	510	His	Ile
Asj	p Gl	y Me		Thi	c Gly	y Gli	520	c Cys	s Trp	o Ile	e Pro	9 Pro 525	Ser	Ser	Asp
Ar	g G1; 53		o Glr	n Gli	ı Ile	e Gl: 53!	ı Gly	y Ası	n Sei	c His	54(Pro	Ser	Туг	Arg

Pro Val Gly Pro Glu Lys Leu His Ser Leu Gln Ser Ala Asn Gly Ser 545 550 555 560

Cys His Glu Arg Ala Pro Asp Leu Pro Arg Gln Thr Glu Pro Val Gln 565 570 575

<210> 118

<211> 550

<212> PRT

<213> Homo sapiens

<400> 118

Met Pro Trp Gly Arg Arg Pro Thr Trp Leu Leu Leu Ala Phe Leu Leu 1 5 10 15

Val Phe Leu Lys Ile Ser Ile Leu Ser Val Thr Ala Trp Gln Thr Gly
20 25 30

Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys
35 40 45

Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser 50 55 60

Arg Ile Asp Pro Asp Gly Thr Asn His Gln Gln Leu Val Val Asp Ala 65 70 75 80

Gly Ile Ser Ala Asp Met Asp Ile His Tyr Lys Lys Glu Arg Leu Tyr 85. 90 95

Trp Val Asp Val Glu Arg Gln Val Leu Leu Arg Val Phe Leu Asn Gly
100 105 110

Thr Gly Leu Glu Lys Val Cys Asn Val Glu Arg Lys Val Ser Gly Leu 115 120 125

Ala Ile Asp Trp Ile Asp Glu Val Leu Trp Val Asp Gln Gln Asn 130 135 140

Gly Val Ile Thr Val Thr Asp Met Thr Gly Lys Asn Ser Arg Val Leu 145 150 155 160

Leu Ser Ser Leu Lys His Pro Ser Asn Ile Ala Val Asp Pro Ile Glu 165 170 175

Arg Leu Met Phe Trp Ser Ser Glu Val Thr Gly Ser Leu His Arg Ala 180 185 190

His Leu Lys Gly Val Asp Val Lys Thr Leu Leu Glu Thr Gly Gly Ile 195 200 205

Ser Val Leu Thr Leu Asp Val Leu Asp Lys Arg Leu Phe Trp Val Gln 210 215 220

Asp Ser Gly Glu Gly Ser His Ala Tyr Ile His Ser Cys Asp Tyr Glu 225 230 235 240

Gly	Gly	Ser	Val	Arg 245	Leu	Ile	Arg	His	Gln 250	Ala	Arg	His	Ser	Leu 255	Ser
Ser	Met	Ala	Phe 260	Phe	Gly	Asp	Arg	Ile 265	Phe	Tyr	Ser	Val	Leu 270	Lys	Ser
Lys	Ala	Ile 275	Trp	Ile	Ala	Asn	Lys 280	His	Thr	Gly	Lys	Asp 285	Thr	Val	Arg
Ile	Asn 290	Leu	His	Pro	Ser	Phe 295	Val	Thr	Pro	Gly	Lys 300	Leu	Met	Val	Val
His 305	Pro	Arg	Ala	Gln	Pro 310	Arg	Thr	Glu	Asp	Ala 315	Ala	Lys	Asp	Pro	Asp 320
Pro	Glu	Leu	Leu	Lys 325	Gln	Arg	Gly	Arg	Pro 330	Cys	Arg	Phe	Gly	Leu 335	Cys
Glu	Arg	Asp	Pro 340	Lys	Ser	His	Ser	Ser 345	Ala	Cys	Ala	Glu	Gly 350	Tyr	Thr
Leu	Ser	Arg 355	Asp	Arg	Lys	Tyr	Cys 360	Glu	Asp	Val	Asn	Glu 365	Cys	Ala	Thr
Gln	Asn 370	His	Gly	Cys	Thr	Leu 375	Gly	Суѕ	Glu	Asn	Thr 380	Pro	Gly	Ser	Tyr
His 385	Cys	Thr	Cys	Pro	Thr 390	Gly	Phe	Val	Leu	Leu 395	Pro	Asp	Gly	Lys	Gln 400
Cys	His	Glu	Leu	Val 405	Ser	Суѕ	Pro	Gly	Asn. 410	Val	Ser	Lys	Cys	Ser 415	His
Gly	Cys	Val	Leu 420	Thr	Ser	Asp	Gly	Pro 425	Arġ	Cys	Ile	Cys	Pro 430	Ala	Gly
		435	Gly				440					445			
Asp	Asn 450	Gly	Gly	Cys	Ser	Gln 455	Ile	Cys	Leu	Pro	Leu 460	Arg	Pro	Gly	Ser
Trp 465	Glu	Cys	Asp	Cys	Phe 470	Pro	Gly	Tyr	Asp	Leu 475	Gln	Ser	Asp	Arg	Lys 480
Ser	Cys	Ala	Ala	Ser 485	Gly	Pro	Gln	Pro	Leu 490	Leu	Leu	Phe	Ala	Asn 495	Ser
Gln	Asp	Ile	Arg 500	His	Met	His	Phe	Asp 505	Gly	Thr	Asp	Tyr	Lys 510	Val	Leu
Leu	Ser	Arg 515	Gln	Met	Gly	Met	Val 520	Phe	Ala	Leu	Asp	Tyr 525		Pro	Val
Glu	Ser 530	_	Ile	Tyr	Phe	Ala 535		Thr	Ala	Leu	Lys 540	Trp	Ile	Glu	Arg
Ala 545		Met	Asp	Gly	Ser 550										

PCT/IL00/00766

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<212> PRT

<213: Homo sapiens

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Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys
35 40 45

Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser 50 55 60

Arg Ile Trp Ala Ile Pro Ser Val Ile Arg Val Asn Lys Arg Thr Gly 65 70 75 80

Gln Asn Arg Val Arg Leu Gln Gly Ser Met Leu Lys Pro Ser Ser Leu 85 90 95

Val Val His Pro Leu Ala Lys Pro Gly Ala Asp Pro Cys Leu Tyr 100 105 110

Arg Asn Gly Gly Cys Glu His Ile Cys Gln Glu Ser Leu Gly Thr Ala 115 120 125

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Cys Ala Phe

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<213> Homo sapiens

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Val Ser Ala Glu Cys Gln Cys Leu Lys Gly Phe Ala Arg Asp Gly Asn 20 25 30

Leu Cys Ser Asp Ile Asp Glu Cys Val Leu Ala Arg Ser Asp Cys Pro 35 40 45

Ser Thr Ser Ser Arg Cys Ile Asn Thr Glu Gly Gly Tyr Val Cys Arg 50 55 60

Cys Ser Glu Gly Tyr Glu Gly Asp Gly Ile Ser Cys Phe Asp Ile Asp 65 70 75 80

Glu Cys Gln Arg Gly Ala His Asn Cys Ala Glu Asn Ala Ala Cys Thr Asn Thr Glu Gly Gly Tyr Asn Cys Thr Cys Ala Gly Arg Pro Ser Ser 105 Pro Gly Leu Ser Cys Pro Asp Ser Thr Ala Pro Ser Leu Leu Gly Glu 120 Asp Gly His His Leu Asp Arg Asn Ser Tyr Pro Gly Cys Pro Ser Ser 135 Tyr Asp Gly Tyr Cys Leu Asn Gly Gly Val Cys Met His Ile Glu Ser Leu Asp Ser Tyr Thr Cys Asn Cys Val Ile Gly Tyr Ser Gly Asp Arg Cys Gln Thr Arg Asp Leu Arg Trp Trp Glu Leu Arg His Ala Gly Tyr 180 185 Gly Gln Lys His Asp Ile Met Val Val Ala Val Cys Met Val Ala Leu Val Leu Leu Leu Leu Gly Met Trp Gly Thr Tyr Tyr Tyr Arg Thr 215 Arg Lys Gln Leu Ser Asn Pro Pro Lys Asn Pro Cys Asp Glu Pro Ser 230 Gly Ser Val Ser Ser Ser Gly Pro Asp Ser Ser Ser Gly Ala Ala Val 245 250 Ala Ser Cys Pro Gln Pro Trp Phe Val Val Leu Glu Lys His Gln Asp 265 Pro Lys Asn Gly Ser Leu Pro Ala Asp Gly Thr Asn Gly Ala Val Val Asp Ala Gly Leu Ser Pro Ser Leu Gln Leu Gly Ser Val His Leu Thr 295 Ser Trp Arg Gln Lys Pro His Ile Asp Gly Met Gly Thr Gly Gln Ser Cys Trp Ile Pro Pro Ser Ser Asp Arg Gly Pro Gln Glu Ile Glu Gly 325 330 Asn Ser His Leu Pro Ser Tyr Arg Pro Val Gly Pro Glu Lys Leu His 345 Ser Leu Gln Ser Ala Asn Gly Ser Cys His Glu Arg Ala Pro Asp Leu 355 360

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Pro Arg Gln Thr Glu Pro Val Gln

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<211> 444

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<213> Homo sapiens

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Asp Tyr Pro Ile Leu Ser Gly Glu Asn Ala Asp Leu Ser Lys Glu Val 20 25 30

Thr Ser Leu Ser Asn Ser Thr Gln Ala Glu Val Pro Asp Asp Gly 35 40 45

Thr Glu Ser Ser Thr Leu Val Ala Glu Ile Met Val Ser Gly Met Asn 50 55 60

Tyr Glu Asp Asp Cys Gly Pro Gly Gly Cys Gly Ser His Ala Arg Cys 65 70 75 80

Val Ser Asp Gly Glu Thr Ala Glu Cys Gln Cys Leu Lys Gly Phe Ala 85 90 95

Arg Asp Gly Asn Leu Cys Ser Asp Ile Asp Glu Cys Val Leu Ala Arg 100 105 110

Ser Asp Cys Pro Ser Thr Ser Ser Arg Cys Ile Asn Thr Glu Gly Gly 115 120 125

Tyr Val Cys Arg Cys Ser Glu Gly Tyr Glu Gly Asp Gly Ile Ser Cys 130 135 140

Phe Asp Ile Asp Glu Cys Gln Arg Gly Ala His Asn Cys Ala Glu Asn 145 150 155 160

Ala Ala Cys Thr Asn Thr Glu Gly Gly Tyr Asn Cys Thr Cys Ala Gly
165 170 175

Arg Pro Ser Ser Pro Gly Leu Ser Cys Pro Asp Ser Thr Ala Pro Ser

Leu Leu Gly Glu Asp Gly His His Leu Asp Arg Asn Ser Tyr Pro Gly 195 200 205

Cys Pro Ser Ser Tyr Asp Gly Tyr Cys Leu Asn Gly Gly Val Cys Met 210 215 220

His Ile Glu Ser Leu Asp Ser Tyr Thr Cys Asn Cys Val Ile Gly Tyr 225 230 235 240

Ser Gly Asp Arg Cys Gln Thr Arg Asp Leu Arg Trp Trp Glu Leu Arg 245 250 255

His Ala Gly Tyr Gly Gln Lys His Asp Ile Met Val Val Ala Val Cys 260 265 270

Met Val Ala Leu Val Leu Leu Leu Leu Gly Met Trp Gly Thr Tyr 275 280 285

Tyr Tyr Arg Thr Arg Lys Gln Leu Ser Asn Pro Pro Lys Asn Pro Cys 290 295 300

Asp Glu Pro Ser Gly Ser Val Ser Ser Ser Gly Pro Asp Ser Ser Ser

315 305 310 Gly Ala Ala Val Ala Ser Cys Pro Gln Pro Trp Phe Val Val Leu Glu 330 325 Lys His Gln Asp Pro Lys Asn Gly Ser Leu Pro Ala Asp Gly Thr Asn 345 340 Gly Ala Val Val Asp Ala Gly Leu Ser Pro Ser Leu Gln Leu Gly Ser 360 Val His Leu Thr Ser Trp Arg Gln Lys Pro His Ile Asp Gly Met Gly 375 Thr Gly Gln Ser Cys Trp Ile Pro Pro Ser Ser Asp Arg Gly Pro Gln 395 390 Glu Ile Glu Gly Asn Ser His Leu Pro Ser Tyr Arg Pro Val Gly Pro 410 Glu Lys Leu His Ser Leu Gln Ser Ala Asn Gly Ser Cys His Glu Arg 420 425 Ala Pro Asp Leu Pro Arg Gln Thr Glu Pro Val Gln 440 <210> 122 <211> 54 <212> PRT <213> Homo sapiens <400> 122 Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp Ala His Ala Thr Glu Glu Ser Gly Asp Ser Arg Ala His Ser Ser Tyr Leu Lys Thr Lys Lys Gly Gln Ser Thr Ser Arg His Ly's Lys Thr Met Val Lys 40 35 Val Gly Pro Asp Ser Asp <210> 123 <211> 855 <212> PRT <213> Homo sapiens <400> 123 Met Lys Tyr Pro Val Trp Pro Arg Tyr Ser Ala Ser Leu Gln Pro Val Val Asp Ser Arg His Leu Thr Val Ala Thr Leu Glu Glu Arg Pro Phe Val Ile Val Glu Ser Pro Asp Pro Gly Thr Gly Gly Cys Val Pro Asn

40

35

Thr Val Pro Cys Arg Arg Gln Ser Asn His Thr Phe Ser Ser Gly Asp Val Ala Pro Tyr Thr Lys Leu Cys Cys Lys Gly Phe Cys Ile Asp Ile 75 Leu Lys Lys Leu Ala Arg Val Val Lys Phe Ser Tyr Asp Leu Tyr Leu Val Thr Asn Gly Lys His Gly Lys Arg Val Arg Gly Val Trp Asn Gly 100 Met Ile Gly Glu Val Tyr Tyr Lys Arg Ala Asp Met Ala Ile Gly Ser Leu Thr Ile Asn Glu Glu Arg Ser Glu Ile Val Asp Phe Ser Val Pro 135 Phe Val Glu Thr Gly Ile Ser Val Met Val Ala Arg Ser Asn Gly Thr 150 Val Ser Pro Ser Ala Phe Leu Glu Pro Tyr Ser Pro Ala Val Trp Val Met Met Phe Val Met Cys Leu Thr Val Val Ala Ile Thr Val Phe Met Phe Glu Tyr Phe Ser Pro Val Ser Tyr Asn Gln Asn Leu Thr Arg Gly 200 Lys Lys Ser Gly Gly Pro Ala Phe Thr Ile Gly Lys Ser Val Trp Leu 215 Leu Trp Ala Leu Val Phe Asn Asn Ser Val Pro Ile Glu Asn Pro Arg 235 230 Gly Thr Thr Ser Lys Ile Met Val Leu Val Trp Ala Phe Phe Ala Val Ile Phe Leu Ala Ser Tyr Thr Ala Asn Leu Ala Ala Phe Met Ile Gln 265 Glu Gln Tyr Ile Asp Thr Val Ser Gly Leu Ser Asp Lys Lys Phe Gln 280 Arg Pro Gln Asp Gln Tyr Pro Pro Phe Arg Phe Gly Thr Val Pro Asn Gly Ser Thr Glu Arg Asn Ile Arg Ser Asn Tyr Arg Asp Met His Thr 315 310 His Met Val Lys Phe Asn Gln Arg Ser Val Glu Asp Ala Leu Thr Ser Leu Lys Met Gly Lys Leu Asp Ala Phe Ile Tyr Asp Ala Ala Val Leu Asn Tyr Met Ala Gly Lys Asp Glu Gly Cys Lys Leu Val Thr Ile Gly 360

Ser Gly Lys Val Phe Ala Thr Thr Gly Tyr Gly Ile Ala Met Gln Lys

	370					375					380				
Asp 385	Ser	His	Trp	Lys	Arg 390	Ala	Ile	Asp	Leu	Ala 395	Leu	Leu	Gln	Phe	Leu 400
Gly	Asp	Gly	Glu	Thr 405	Gln	Lys	Leu	Glu	Thr 410	Val	Trp	Leu	Ser	Gly 415	Ile
Cys	Gln	Asn	Glu 420	Lys	Asn	Glu	Val	Met 425	Ser	Ser	Lys	Leu	Asp 430	Ile	Asp
Asn	Met	Ala 435	Gly	Val	Phe	Tyr	Met 440	Leu	Leu	Val	Ala	Met 445	Gly	Leu	Ala
Leu	Leu 450	Val	Phe	Ala	Trp	Glu 455	His	Leu	Val	Tyr	Trp 460	Lys	Leu	Arg	His
465			Asn		470					475					480
			Ser	485					490					495	
			Ser 500					505					510		
		515					520					525			
	530		Leu			535					540				
545			Ala		550					555					560
			Cys	565					570					5/5	
								585	i				590		
		595					600)				605)		
	610)	Arg			615					620)			
625	,		Gly		630	l				635	•				640
			Ala	645					650)				655	
			9 Pro 660)				665	5				6/()	
		675					680)				685)		
Let	ı His		a Ala	Trp	Ala	Arg 695	g Gly	y Sei	r Ar	g Pro	700	g His O	s Ala	a Ser	: Leu

Pro Ser Ser Val Ala Glu Ala Phe Ala Arg Pro Ser Ser Leu Pro Ala 710 715 Gly Cys Thr Gly Pro Ala Cys Ala Arg Pro Asp Gly His Ser Ala Cys 730 Arg Arg Leu Ala Gln Ala Gln Ser Met Cys Leu Pro Ile Tyr Arg Glu Ala Cys Gln Glu Gly Glu Gln Ala Gly Ala Pro Ala Trp Gln His Arg Gln His Val Cys Leu His Ala His Ala His Leu Pro Phe Cys Trp Gly Ala Val Cys Pro His Leu Pro Pro Cys Ala Ser His Gly Ser Trp Leu 795 790 Ser Gly Ala Trp Gly Pro Leu Gly His Arg Gly Arg Thr Leu Gly Leu Gly Thr Gly Tyr Arg Asp Ser Gly Gly Leu Asp Glu Ile Ser Xaa Val Ala Arg Gly Thr Gln Gly Phe Pro Gly Pro Cys Thr Trp Arg Arg Ile Ser Ser Leu Glu Ser Glu Val 850 <210> 124 <211> 665 <212> PRT <213> Homo sapiens <400> 124 Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr 75 Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu 90 85 Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr 105 Phe Tyr Tyr Ala Val Ala Val Lys Lys Asp Ser Gly Phe Gln Met

120

115

Asn	Gln 130	Leu	Arg	Gly	Lys	Lys 135	Ser	Cys	His	Thr	Gly 140	Leu	Gly	Arg	Ser
Ala 145	Gly	Trp	Asn	Ile	Pro 150	Ile	Gly	Leu	Leu	Tyr 155	Cys	Asp	Leu	Pro	Glu 160
Pro	Arg	Lys	Pro	Leu 165	Glu	Lys	Ala	Val	Ala 170	Asn	Phe	Phe	Ser	Gly 175	Ser
Cys	Ala	Pro	Cys 180	Ala	Asp	Gly	Thr	Asp 185	Phe	Pro	Gln	Leu	Cys 190	Gln	Leu
Cys	Pro	Gly 195	Cys	Gly	Cys	Ser	Thr 200	Leu	Asn	Gln	Tyr	Phe 205	Gly	Tyr	Ser
Gly	Ala 210	Phe	Lys	Суз	Leu	Lys 215	Asp	Gly	Ala	Gly	Asp 220	Val	Ala	Phe	Val
Lys 225	His	Ser	Thr	Ile	Phe 230	Glu	Asn	Leu	Ala	Asn 235	Lys	Ala	Asp	Arg	Asp 240
Gln	Tyr	Glu	Leu	Leu 245	Cys	Leu	Asp	Asn	Thr 250	Arg	Lys	Pro	Val	Asp 255	Glu
Tyr	Lys	Asp	Cys 260	.His	Leu	Ala	Gln	Val 265	Pro	Ser	His	Thr	Val 270	Val	Ala
Arg	Ser	Met 275	Gly	Gly	Lys	Glu	Asp 280	Leu	Ile	Trp	Glu	Leu 285	Leu	Asn	Gln
Ala	Gln 290	Glu	His	Phe	Gly	Lys 295	Asp	Lys	Ser	Lys	Glu 300	Phe	Gln	Leu	Phe
Ser 305	Ser	Pro	His	Gly	Lys 310	Asp	Leu	Leu	Phe	Lys 315	Asp	Ser	Ala	His	Gly 320
Phe	Leu	Lys	Val	Pro 325	Pro	Arg	Met	Asp	Ala 330	Lys	Met	Tyr	Leu	Gly 335	Tyr
Glu	Tyr	Val	Thr 340	Ala	Ile	Arg	Asn	Leu 345	Arg	Glu	Gly	Thr	Cys 350	Pro	Glu
Ala	Pro	Thr 355	Asp	Glu	Cys	Lys	Pro 360	Val	Lys	Trp	Cys	Ála 365	Leu	Ser	His
His	Glu 370	Arg	Leu	Lys	Cys	Asp 375	Glu	Trp	Ser	Val	Asn 380	Ser	Val	Gly	Lys
Ile 385		Cys	Val	Ser	Ala 390	Glu	Thr	Thr	Glu	Asp 395	Cys	Ile	Ala	Lys	11e 400
Met	Asn	Gly	Glu	Ala 405	Asp	Ala	Met	Ser	Leu 410	Asp	Gly	Gly	Phe	Val 415	Tyr
Ile	Ala	Gly	Lys 420		Gly	Leu	Val	Pro 425		Leu	Ala	Glu	Asn 430	Tyr	Asn
Lys	Ser	Asp 435		Cys	Glu	Asp	Thr 440	Pro	Glu	Ala	Gly	Tyr 445	Phe	Ala	Val

Ala	Val 450	Val	Lys	Lys	Ser	A1a 455	Ser	Asp	Leu	Thr	Trp 460	Asp	Asn	Leu	Lys
Gly 465	Lys	Lys	Ser	Cys	His 470	Thr	Ala	Phe	Gly	Arg 4 75	Thr	Ala	Gly	Trp	Asr 480
Ile	Pro	Met	Gly	Leu 485	Leu	Tyr	Asn	Lys	Ile 490	Asn	His	Cys	Arg	Phe 495	Asp
Glu	Phe	Phe	Ser 500	Glu	Gly	Cys	Ala	Pro 505	Gly	Ser	Lys	Lys	Asp 510	Ser	Ser
Leu	Cys	Lys 515	Leu	Cys	Met	Gly	Ser 520	Gly	Leu	Asn	Leu	Cỳs 525	Glu	Pro	Asr
Asn	Lys 530	Glu	Gly	Tyr	Tyr	Gly 535	Tyr	Thr	Gly	Ala	Phe 540	Arg	Cys	Leu	Val
Glu 545	Lys	Gly	Asp	Val	Ala 550	Phe	Val	Lys	His	Gln 555	Thr	Val	Pro	Gln	Asr 560
Thr	Gly	Gly	Lys	Asn 565	Pro	Asp	Pro	Trp	Ala 570	Lys	Asn	Leu	Asn	Glu 575	Lys
Asp	Tyr	Glu	Leu 580	Leu	Cys	Leu	Asp	Gly 585	Thr	Arg	Lys	Pro	Val 590	Glu	Glu
Tyr	Ala	Asn 595	Cys	His	Leu	Ala	Arg 600	Ala	Pro	Asn	His	Ala 605	Val	Val	Thr
Arg	Lys 610	Asp	Lys	Glu	Ala	Cys 615	Val	His	Lys	Ile	Leu 620	Arg	Gln	Gln	Gln
His 625	Leu	Phe	Gly	Ser	Asn 630	Val	Thr	Asp	Суѕ	Ser 635	Gly	Asn	Phe	Суѕ	Leu 640
Phe	Arg	Ser	Glu	Thr 645	Lys	Asp	Leu	Leu	Phe 650	Arg	Asp	Asp	Thr	His 655	Leu
Leu	Glu	Ala	Cys 660	Thr	Phe	Arg	Arg	Pro 665	:						
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Cys	Leu	Ala	Val 20	Pro	Asp	Lys	Thr	Val 25	Arg	Trp	Cys	Ala	Val 30	Ser	Glu
His	Glu	Ala 35	Thr	Lys	Cys	Gln	Ser 40	Phe	Arg	Asp	His	Met 45	Lys	Ser	Val

Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr 50 55 60

Leu 65	Asp	Cys	Ile	Arg	Ala 70	Ile	Ala	Ala	Asn	Glu 75	Ala	Asp	Ala	Val	Thr 80
	Asp	Ala	Gly	Leu 85	Val	Tyr	Asp	Ala	Tyr 90	Leu	Ala	Pro	Asn	Asn 95	Leu
Lys	Pro	Val	Val	Ala	Glu	Phe	Tyr	Gly 105		Lys	Glu	Asp	Pro	Gln	Thr
Phe	Tyr	Tyr 115		Val	Ala	Val	Val 120		Lys	Asp	Ser	Gly 125	Phe	Gln	Met
Asn	Gln 130		Arg	Gly	Lys	Lys 135		Cys	His	Thr	Gly 140	Leu	Gly	Arg	Ser
Ala 145		Trp	Asn	Ile	Pro 150		Gly	Leu	Leu	Tyr 155	Cys	Asp	Leu	Pro	Glu 160
	Arg	Lys	Pro	Leu 165	Glu	Lys	Ala	Val	Ala 170	Asn	Phe	Phe	Ser	Gly 175	Ser
Cys	Ala	Pro	Cys 180	Ala	Asp	Gly	Thr	Asp 185	Phe	Pro	Gln	Leu	Cys 190	Gln	Leu
Cys	Pro	Gly 195	Cys	Gly	Cys	Ser	Thr 200	Leu	Asn	Gln	Tyr	Phe 205	Gly	Tyr	Ser
Gly	Ala 210		Lys	Cys	Leu	Lys 215	Asp	Gly	Ala	Gly	Asp 220	Val	Ala	Phe	Val
Lys 225		Ser	Thr	Ile	Phe 230	Glu	Asn	Leu	Ala	Asn 235	Lys	Ala	Asp	Arg	Asp 240
Gln	Tyr	Glu	Leu	Leu 245	Cys	Leu	Asp	Asn	Thr 250	Arg	Lys	Pro	Val	Asp 255	Glu
Tyr	Lys	Asp	Cys 260	His	Leu	Ala	Gln	Val 265	Pro	Ser	His	Thr	Val 270	Val	Ala
Arg	Ser	Met 275		Gly	Lys	Glu	Asp 280	Leu	Ile	Trp	Glu	Leu 285	Leu	Asn	Gln
Ala	Gln 290		His	Phe	Gly	Lys 295		Lys	Ser	Lys	Glu 300	Phe	Gln	Leu	Phe
Ser 305		Pro	His	Gly	Lys 310		Leu	Leu	Phe	2 Lys 315	a Asp	Ser	Ala	His	Gl ₃ 320
Phe	e Le	ı Lys	s Val	. Pro		Arg	y Met	. Asp	Ala 330		s Met	Туг	Leu	Gly 335	Туг
Glu	туі	r Val	L Thr 340	Ala	Ile	Arç	g Asr	1 Leu 345		g Glu	ı Gly	/ Thi	Cys 350	Pro	Glu
Ala	a Pro	o Thi 35		o Glu	ı Cys	Lys	360	Val	Lys	s Trį	р Суз	365	a Lev	ı Ser	His
His	s Gl:		g Lev	ı Lys	s Cys	37		ı Trp	Se:	r Val	1 Asr 380	n Sei	c Val	L Gly	/ Ly:
Ile	e Gl	u Cy:	s Vai	l Sei	Ala	a Gl	ı Thi	c Thi	c Gl	u Ası	p Cys	s Ile	e Ala	a Lys	3 Il

385 390 395 Met Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Phe Val Tyr 405 410 Ile Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr Asn 420 425 Lys Ser Asp Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala Glu 440 Glu Gly Cys Ala Pro Gly Ser Lys Lys Asp Ser Ser Leu Cys Lys Leu 455 Cys Met Gly Ser Gly Leu Asn Leu Cys Glu Pro Asn Asn Lys Glu Gly 470 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Val Glu Lys Gly Asp 490 Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn Thr Gly Gly Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu Lys Asp Tyr Glu Leu 520 Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu Tyr Ala Asn Cys 535 His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr Arg Lys Asp Lys 545 550 Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln His Leu Phe Gly 570 565 Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu Phe Arg Ser Glu 585 Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys Leu Ala Lys Leu 600 His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu Glu Tyr Val Lys 615 Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser Leu Leu Glu Ala 625 Cys Thr Phe Arg Arg Pro 645 <210> 126 <211> 4787 <212> PRT <213> Homo sapiens

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Thr Glu Asp Glu Val Val Leu Gln Cys Ile Ala Thr Ile His Lys Glu

25

30

20

Gln Arg Lys Phe Cys Leu Ala Ala Glu Gly Leu Gly Asn Arg Leu Cys

Phe Leu Glu Pro Thr Ser Glu Ala Lys Tyr Ile Pro Pro Asp Leu Cys

Val Cys Asn Phe Val Leu Glu Gln Ser Leu Ser Val Arg Ala Leu Gln

Glu Met Leu Ala Asn Thr Gly Glu Asn Gly Glu Gly Ala Ala Gln

Gly Gly Gly His Arg Thr Leu Leu Tyr Gly His Ala Val Leu Leu Arg

His Ser Phe Ser Gly Met Tyr Leu Thr Cys Leu Thr Thr Ser Arg Ser 120

Gln Thr Asp Lys Leu Ala Phe Asp Val Gly Leu Arg Glu His Ala Thr

Gly Glu Ala Cys Trp Trp Thr Ile His Pro Ala Ser Lys Gln Arg Ser 150

Glu Gly Glu Lys Val Arg Ile Gly Asp Asp Leu Ile Leu Val Ser Val 170

Ser Ser Glu Arg Tyr Leu His Leu Ser Val Ser Asn Gly Asn Ile Gln

Val Asp Ala Ser Phe Met Gln Thr Leu Trp Asn Val His Pro Thr Cys 200

Ser Gly Ser Ser Ile Glu Glu Gly Tyr Leu Leu Gly Gly His Val Val 215

Arg Leu Phe His Gly His Asp Glu Cys Leu Thr Ile Pro Ser Thr Asp 235

Gln Asn Asp Ser Gln His Arg Arg Ile Phe Tyr Glu Ala Gly Gly Ala 250

Gly Thr Arg Ala Xaa Ser Leu Trp Arg Val Glu Pro Leu Arg Ile Ser - 260

Trp Ser Gly Ser Asn Ile Arg Trp Gly Gln Ala Phe Arg Leu Arg His 280

Leu Thr Thr Gly His Tyr Leu Ala Leu Thr Glu Asp Gln Gly Leu Ile 290

Leu Gln Asp Arg Ala Lys Ser Asp Thr Lys Ser Thr Ala Phe Ser Phe 315 310

Arg Ala Ser Lys Glu Leu Lys Glu Lys Leu Asp Ser Ser His Lys Arg 330

Asp Ile Glu Gly Met Gly Val Pro Glu Ile Lys Tyr Gly Asp Ser Val 345 340

Cys	Phe	Val 355	Gln	His	Ile	Ala	Ser 360	Gly	Leu	Trp	Val	Thr 365	Tyr	Lys	Ala
Gln	Asp 370	Ala	Lys	Thr	Ser	Arg 375	Leu	Gly	Pro	Leu	Lys 380	Arg	Lys	Val	Ile
Leu 385	His	Gln	Glu	Gly	His 390	Met	Asp	Asp	Gly	Leu 395	Thr	Leu	Gln	Arg	Cys 400
Gln	Arg	Glu	Glu	Ser 405	Gln	Ala	Ala	Arg	Ile 410	Ile	Arg	Asn	Thr	Thr 415	Ala
Leu	Phe	Ser	Gln 420	Phe	Val	Ser	Gly	Asn 425	Asn	Arg	Thr	Ala	Ala 430	Pro	Ile
Thr	Leu	Pro 435	Ile	Glu	Glu	Val	Leu 440	Gln	Thr	Leu	Gln	Asp 445	Leu	Ile	Ala
Tyr	Phe 450	Gln	Pro	Pro	Glu	Glu 45 5	Glu	Met	Arg	His	Glu 460	Asp	Lys	Gln	Asn
Lys 465	Leu	Arg	Ser	Leu	Lys 470	Asn	Arg	Gln	Asn	Leu 475	Phe	Lys	Glu	Glu	Gly 480
Met	Leu	Ala	Leu	Val 485	Leu	Asn	Cys	Ile	Asp 490	Arg	Leu	Asn	Xaa	Tyr 495	Asn
Ser	Val	Ala	His 500	Phe	Ala	GÏy	Ile	Ala 505	Arg	Glu	Glu	Ser	Gly 510	Met	Ala
Trp	Lys	Glu 515	Ile	Leu	Asn	Leu	Leu 520	Tyr	Lys	Leu	Leu	Ala 525	Ala	Leu	Ile
Arg	Gly 530	Asn	Arg	Asn	Asn	Cys 535	Ala	Gln	Phe	Ser	Asn 540	Asn	Leu	Asp	Trp
Leu 545	Ile	Ser	Lys	Leu	Asp 550	Arg	Leu	Glu	Ser	Ser 555	Ser	Gly	Ile	Leu	Glu 560
Val	Leu	His	Cys	Ile 565	Leu	Thr	Glu	Ser	Pro 570	Ģlu	Ala	Leu	Asn	Leu 575	Ile
Ala	Glu	Gly	His 580	Ile	Lys	Ser	Ile	Ile 585	Ser	Leu	Leu	Asp	Lys 590	His	Gly
Arg	Asn	His 595	Lys	Val	Leu	Asp	Ile 600	Leu	Cys	Ser	Leu	Cys 605	Leu	Суѕ	Asn
Gly	Val 610	Ala	Val	Arg	Ala	Asn 615	Gln	Asn	Leu	Ile	Cys 620	Asp	Asn	Leu	Leu
Pro 625	Arg	Arg	Asn	Leu	Leu 630	Leu	Gln	Thr	Arg	Leu 635	Ile	Asn	Asp	Val	Thr 640
Ser	Ile	Arg	Pro	Asn 645	Ile	Phe	Leu	Gly	Val 650	Ala	Glu	Gly	Ser	Ala 655	Gln
Tyr	Lys	Lys	Trp 660	Tyr	Phe	Glu	Leu	Ile 665	Ile	Asp	Gln	Val	Asp 670	Pro	Phe

Leu Thr Ala Glu Pro Thr His Leu Arg Val Gly Trp Ala Ser Ser Ser Gly Tyr Ala Pro Xaa Pro Gly Gly Gly Glu Gly Trp Gly Gly Asn Gly Val Gly Asp Asp Leu Tyr Ser Tyr Gly Phe Asp Gly Leu His Leu Trp Ser Gly Arg Ile Pro Arg Ala Val Ala Ser Xaa Asn Gln His Leu Leu 730 Arg Ser Asp Asp Val Val Ser Cys Cys Leu Asp Leu Gly Cys Pro Ala Ser His Ser Ala Ser Met Gly Ser Pro Cys Arg Gly Cys Leu Arg Asn 760 Phe Asn Thr Asp Gly Leu Phe Phe Pro Val Met Ser Phe Ser Ala Gly 775 Val Lys Val Arg Phe Leu Met Gly Gly Arg His Gly Glu Phe Lys Phe 790 Leu Pro Pro Ser Gly Tyr Ala Pro Cys Tyr Glu Ala Leu Leu Pro Lys 810 Glu Lys Met Arg Leu Glu Pro Val Lys Glu Tyr Lys Arg Asp Ala Asp Gly Ile Arg Asp Leu Leu Gly Thr Thr Gln Phe Leu Ser Gln Ala Ser 840 Phe Ile Pro Cys Pro Val Asp Thr Ser Gln Val Ile Leu Pro Pro His 855 Leu Glu Lys Ile Arg Asp Arg Leu Ala Glu Asn Ile His Glu Leu Trp 870 Gly Met Asn Lys Ile Glu Leu Gly Trp Thr Phe Gly Lys Ile Arg Asp 890 Asp Asn Lys Arg Gln His Pro Cys Leu Val Glu Phe Ser Lys Leu Pro Glu Thr Glu Lys Asn Tyr Asn Leu Gln Met Ser Thr Glu Thr Leu Lys 920 Thr Leu Leu Xaa Leu Gly Cys His Ile Ala His Val Asn Pro Ala Ala 935 Glu Glu Asp Leu Lys Lys Val Lys Leu Pro Lys Asn Tyr Met Met Ser 950 945 Asn Gly Tyr Lys Pro Ala Pro Leu Asp Leu Ser Asp Val Lys Leu Leu 970 Pro Pro Gln Glu Ile Leu Val Asp Lys Leu Ala Glu Asn Ala His Asn Val Trp Ala Lys Asp Arg Ile Lys Gln Gly Trp Thr Tyr Gly Ile Gln 995 1000 1005

Gln Asp Leu Lys Asn Lys Arg Asn Pro Arg Leu Val Pro Tyr Ala Leu 1010 1015 1020

- Leu Asp Glu Arg Thr Lys Lys Ser Asn Arg Asp Ser Leu Arg Glu Ala 1025 1030 1035 1040
- Val Arg Thr Phe Val Gly Tyr Gly Tyr Asn Ile Glu Pro Ser Asp Gln 1045 1050 1055
- Glu Leu Ala Asp Ser Ala Val Glu Lys Val Ser Ile Asp Lys Ile Arg 1060 1065 1070
- Phe Phe Arg Val Glu Arg Ser Tyr Xaa Val Arg Ser Gly Lys Trp Tyr 1075 1080 1085
- Phe Glu Phe Glu Val Val Thr Gly Gly Asp Met Arg Val Gly Trp Ala 1090 1095 1100
- Arg Pro Gly Cys Arg Pro Asp Val Glu Leu Gly Ala Asp Asp Gln Ala 1105 1110 1115 1120
- Phe Val Phe Glu Gly Asn Arg Gly Gln Arg Trp His Gln Gly Ser Gly 1125 1130 1135
- Tyr Phe Gly Arg Thr Trp Gln Pro Gly Asp Val Val Gly Cys Met Ile 1140 1145 1150
- Asn Leu Asp Asp Ala Ser Met Ile Phe Thr Leu Asn Gly Glu Leu Leu 1155 1160 1165
- Ile Thr Asn Lys Gly Ser Glu Leu Ala Phe Ala Asp Tyr Glu Ile Glu 1170 1175 1180
- Asn Gly Phe Val Pro Ile Cys Cys Leu Gly Leu Ser Gln Ile Gly Arg 1185 1190 1195 1200
- Met Asn Leu Gly Thr Asp Ala Ser Thr Phe Lys Phe Tyr Thr Met Cys 1205 1210 1215
- Gly Leu Gln Glu Gly Phe Glu Pro Phe Ala Val Asn Met Asn Arg Asp 1220 1225 1230
- Val Ala Met Trp Phe Ser Lys Arg Leu Pro Thr Phe Val Asn Val Pro 1235 1240 1245
- Lys Asp His Pro His Ile Glu Val Met Arg Ile Asp Gly Thr Met Asp 1250 1255 1260 .
- Ser Pro Pro Cys Leu Lys Val Thr His Lys Thr Phe Gly Thr Gln Asn 1265 1270 1275 1280
- Ser Asn Ala Asp Met Ile Tyr Cys Arg Leu Ser Met Pro Val Glu Cys 1285 1290 1295
- His Ser Ser Phe Ser His Ser Pro Cys Leu Asp Ser Glu Ala Phe Gln 1300 1305 1310
- Lys Arg Lys Gln Met Gln Glu Ile Leu Ser His Thr Thr Gln Cys 1315 1320 1325

Tyr Tyr Ala Ile Arg Ile Phe Xaa Gly Gln Asp Pro Ser Cys Val Trp 1330 1335 1340

- Val Gly Trp Val Thr Pro Asp Tyr His Leu Tyr Ser Glu Lys Phe Asp 1345 1350 1355 1360
- Leu Asn Lys Asn Cys Thr Val Thr Val Thr Leu Gly Asp Glu Arg Gly 1365 1370 1375
- Arg Val His Glu Ser Val Lys Arg Ser Asn Cys Tyr Met Val Trp Gly 1380 1385 1390
- Gly Asp Ile Val Ala Ser Ser Gln Arg Ser Asn Arg Ser Asn Val Asp 1395 1400 1405
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- Ser Ala Asn Gly Lys Glu Leu Gly Thr Cys Tyr Gln Val Glu Pro Asn 1425 1430 1435 1440
- Thr Lys Val Phe Pro Ala Val Phe Leu Gln Pro Thr Ser Thr Ser Leu 1445 1450 1455
- Phe Gln Phe Glu Leu Gly Lys Leu Lys Asn Ala Met Pro Leu Ser Ala 1460 1465 1470
- Ala Ile Phe Arg Ser Glu Glu Xaa Asn Pro Val Pro Gln Cys Pro Pro 1475 1480 1485
- Arg Leu Asp Val Gln Thr Ile Gln Pro Val Leu Trp Ser Arg Met Pro 1490 1495 1500
- Asn Ser Phe Leu Lys Val Glu Thr Glu Arg Val Ser Glu Arg His Gly 1505 1510 1515 1520
- Trp Val Val Gln Cys Leu Glu Pro Leu Gln Met Met Ala Leu His Ile 1525 1530 1535
- Pro Glu Glu Asn Arg Cys Val Asp Ile Leu Glu Leu Cys Glu Gln Glu 1540 1545 1550
- Asp Leu Met Arg Phe His Tyr His Thr Leu Arg Leu Tyr Ser Ala Val 1555 1560 1565
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- Asp Leu Ser Gln Leu Phe Tyr Ala Ile Asp Asn Lys Tyr Leu Pro Gly 1585 1590 1595 1600
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- Ile Thr Ser Thr Thr Arg Asn Ile Cys Leu Phe Pro Asp Glu Ser Lys 1635 1640 1645

Arg His Gly Leu Pro Gly Val Gly Leu Arg Thr Cys Leu Lys Pro Gly 1650 1660

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- Lys Gln Ser Pro Glu Ile Pro Leu Glu Ser Leu Arg Thr Lys Ala Leu 1685 1690 1695
- Ser Met Leu Thr Glu Ala Val Gln Cys Ser Gly Ala His Ile Arg Asp 1700 1705 1710
- Pro Val Gly Gly Ser Val Glu Phe Gln Phe Val Pro Val Leu Lys Leu 1715 1720 1725
- Ile Gly Thr Leu Leu Val Met Gly Val Phe Asp Asp Asp Val Arg 1730 1740
- Gln Ile Leu Leu Ile Asp Pro Ser Val Phe Gly Glu His Ser Ala 1745 1750 1755 1760
- Gly Thr Glu Glu Gly Ala Glu Lys Glu Glu Val Thr Gln Val Glu Glu 1765 1770 1775
- Lys Ala Val Glu Ala Gly Glu Lys Ala Gly Lys Glu Ala Pro Val Lys 1780 1785 1790
- Gly Leu Leu Gln Thr Arg Leu Pro Glu Ser Val Lys Leu Gln Met Cys 1795 1800 1805
- Glu Leu Leu Ser Tyr Leu Cys Asp Cys Glu Leu Gln His Arg Val Glu 1810 1815 1820
- Ala Ile Val Ala Phe Gly Asp Ile Tyr Val Ser Lys Leu Gln Ala Asn 1825 1830 1835 1840
- Gln Lys Phe Arg Tyr Asn Glu Leu Met Gln Ala Leu Asn Met Ser Ala 1845 1850 1855
- Ala Leu Thr Ala Arg Lys Thr Lys Glu Phe Arg Ser Pro Pro Gln Glu 1860 1865 1870
- Gln Ile Asn Met Leu Leu Asn Phe Gln Leu Gly Glu Asn Cys Pro Cys 1875 1880 1885
- Pro Glu Glu Ile Arg Glu Glu Leu Tyr Asp Phe His Glu Asp Leu Leu 1890 1895 1900
- Leu His Cys Gly Val Pro Leu Glu Glu Glu Glu Glu Glu Glu Glu Glu Asp 1905 1910 1915 1920
- Thr Ser Trp Thr Gly Lys Leu Cys Ala Leu Val Tyr Lys Ile Lys Gly 1925 1930 1935
- Pro Pro Lys Pro Glu Lys Glu Gln Pro Thr Glu Glu Glu Glu Arg Cys 1940 1945 1950
- Pro Thr Thr Leu Lys Glu Leu Ile Ser Gln Thr Met Ile Cys Trp Ala 1955 1960 1965
- Gln Glu Asp Gln Ile Gln Asp Ser Glu Leu Val Arg Met Met Phe Asn

1970 1975 1980

Leu Leu Arg Arg Gln Tyr Asp Ser Ile Gly Glu Leu Leu Gln Ala Leu 1985 1990 1995 2000

- Arg Lys Thr Tyr Thr Ile Ser His Thr Ser Val Ser Asp Thr Ile Asn 2005 2010 2015
- Leu Leu Ala Ala Leu Gly Gln Ile Arg Ser Leu Leu Ser Val Arg Met 2020 2025 2030
- Gly Lys Glu Glu Glu Leu Leu Met Ile Asn Gly Leu Gly Asp Ile Met
 2035 2040 2045
- Asn Asn Lys Val Phe Tyr Gln His Pro Asn Leu Met Arg Val Leu Gly 2050 2055 2060
- Met His Glu Thr Val Met Glu Val Met Val Asn Val Leu Gly Thr Glu 2065 2070 2075 2080
- Lys Ser Gln Ile Ala Phe Pro Lys Met Val Ala Ser Cys Cys Arg Phe 2085 2090 2095
- Leu Cys Tyr Phe Cys Arg Ile Ser Arg Gln Asn Gln Lys Ala Met Phe 2100 2105 2110
- Glu His Leu Ser Tyr Leu Leu Glu Asn Ser Ser Val Gly Leu Ala Ser 2115 2120 2125
- Pro Ser Met Arg Gly Ser Thr Pro Leu Asp Val Ala Ala Ser Ser Val 2130 2135 2140
- Met Asp Asn Asn Glu Leu Ala Leu Ser Leu Glu Glu Pro Asp Leu Glu 2145 2150 2155 2160
- Lys Val Val Thr Tyr Leu Ala Gly Cys Gly Leu Gln Ser Cys Pro Met 2165 2170 2175
- Leu Leu Ala Lys Gly Tyr Pro Asp Val Gly Trp Asn Pro Ile Glu Gly 2180 2185 : 2190
- Glu Arg Tyr Leu Ser Phe Leu Arg Phe Ala Val Phe Val Asn Ser Glu 2195 2200 2205
- Ser Val Glu Glu Asn Ala Ser Val Val Val Lys Leu Leu Ile Arg Arg 2210 2215 2220
- Pro Glu Cys Phe Gly Pro Ala Leu Arg Gly Glu Gly Gly Asn Gly Leu 2225 2230 2235 2240
- Leu Ala Ala Met Gln Gly Ala Ile Lys Ile Ser Glu Asn Pro Ala Leu 2245 2250 2255
- Asp Leu Pro Ser Gln Gly Tyr Lys Arg Glu Val Ser Thr Glu Asp Asp 2260 2265 2270
- Glu Glu Glu Glu Glu Ile Val His Met Gly Asn Ala Ile Met Ser Phe 2275 2280 2285
- Tyr Ser Ala Leu Ile Asp Leu Leu Gly Arg Cys Ala Pro Glu Met His 2290 2295 2300

Leu Ile Gln Thr Gly Lys Gly Glu Ala Ile Arg Ile Arg Ser Ile Leu 2305 2310 2315 2320

- Arg Ser Leu Val Pro Thr Glu Asp Leu Val Gly Ile Ile Ser Ile Pro 2325 2330 2335
- Leu Lys Leu Pro Ser Leu Asn Lys Asp Gly Ser Val Ser Glu Pro Asp 2340 2345 2350
- Met Ala Xaa Asn Phe Cys Pro Asp His Lys Ala Pro Met Val Leu Phe 2355 2360 2365
- Leu Asp Arg Val Tyr Gly Ile Lys Asp Gln Thr Phe Leu Leu His Leu 2370 2375 2380
- Leu Glu Val Gly Phe Leu Pro Asp Leu Arg Ala Ser Ala Ser Leu Asp 2385 2390 2395 2400
- Thr Val Ser Leu Ser Thr Thr Glu Ala Ala Leu Ala Leu Asn Arg Tyr 2405 2410 2415
- Ile Cys Ser Ala Val Leu Pro Leu Leu Thr Arg Cys Ala Pro Leu Phe 2420 2425 2430
- Xaa Gly Thr Glu His Cys Thr Ser Leu Ile Asp Ser Thr Leu Gln Thr 2435 2440 2445
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- Met Leu Gln Gln Leu Leu Arg Arg Leu Val Phe Asp Val Pro Gln Leu 2485 2490 2495
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- Gln Cys Trp Lys Tyr Tyr Cys Leu Pro Ser Gly Trp Gly Ser Tyr Gly 2515 2520 2525
- Leu Ala Val Glu Glu Glu Leu His Leu Thr Glu Lys Leu Phe Trp Gly 2530 2540
- Ile Xaa Asp Ser Leu Ser His Lys Lys Tyr Asp Pro Asp Leu Phe Arg 2545 2550 2555 2560
- Met Ala Leu Pro Cys Leu Ser Ala Ile Ala Gly Ala Leu Pro Pro Asp 2565 2570 2575
- Tyr Leu Asp Xaa Arg Ile Thr Ala Thr Leu Glu Lys Gln Ile Ser Val 2580 $2585 \cdot 2590$
- Asp Ala Asp Gly Asn Phe Asp Pro Lys Pro Ile Asn Thr Met Asn Phe 2595 2600 2605
- Ser Leu Pro Glu Lys Leu Glu Tyr Ile Val Thr Lys Tyr Ala Glu His 2610 2615 2620

Ser His Asp Lys Trp Ala Cys Asp Lys Ser Gin Ser Gly Trp Lys Tyr 2625 2630 2635 2640

- Gly Ile Ser Leu Asp Glu Asn Val Lys Thr His Pro Leu Ile Arg Pro 2645 2650 2655
- Phe Lys Thr Leu Thr Glu Lys Glu Lys Glu Ile Tyr Arg Trp Pro Ala 2660 2665 2670
- Arg Glu Ser Leu Lys Thr Met Leu Ala Val Gly Trp Thr Val Glu Arg 2675 2680 2685
- Thr Lys Glu Gly Glu Ala Leu Val Gln Gln Arg Glu Asn Glu Lys Leu 2690 2695 2700
- Arg Ser Val Ser Gln Ala Asn Gln Gly Asn Ser Tyr Ser Pro Ala Pro 2705 2710 2715 2720
- Leu Asp Leu Ser Asn Val Val Leu Ser Arg Glu Leu Gln Gly Met Val 2725 2730 2735
- Glu Val Val Ala Glu Asn Tyr His Asn Ile Trp Ala Lys Lys Lys 2740 2745 2750
- Leu Glu Leu Glu Ser Lys Gly Gly Gly Ser His Pro Leu Leu Val Pro 2755 2760 2765
- Tyr Asp Thr Leu Thr Ala Lys Glu Lys Phe Lys Asp Arg Glu Lys Ala 2770 2785
- Gln Asp Leu Phe Lys Phe Leu Gln Val Asn Gly Ile Ile Val Ser Arg 2785 2790 2795 2800
- Gly Met Lys Asp Met Glu Leu Asp Ala Ser Ser Met Glu Lys Arg Phe 2805 2810 2815
- Xaa Tyr Lys Phe Leu Lys Lys Ile Leu Lys Tyr Val Asp Ser Ala Gln 2820 2825 2830
- Glu Phe Ile Ala His Leu Glu Ala Ile Val Ser Ser Gly Lys Thr Glu 2835 2840 2845
- Lys Ser Pro Arg Asp Gln Glu Ile Lys Phe Phe Ala Lys Val Leu Leu: 2850 2855 2860
- Pro Leu Val Asp Gln Tyr Phe Thr Ser His Cys Leu Tyr Phe Leu Ser 2865 2870 2875 2880
- Ser Pro Leu Lys Pro Leu Ser Ser Ser Gly Tyr Ala Ser His Lys Glu 2885 2890 2895
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- Leu His Ile Leu Ala Gln Thr Leu Asp Thr Arg Thr Val Met Lys Ser 2930 2940
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2945 2950 2955 2960

Ala Glu Asp Leu Glu Lys Thr Ser Glu Asn Leu Lys Leu Gly Lys Phe 2965 2970 2975

Thr His Ser Arg Thr Gln Ile Lys Gly Val Ser Gln Asn Ile Asn Tyr 2980 2985 2990

Thr Thr Val Ala Leu Leu Pro Ile Leu Thr Ser Ile Phe Glu His Val 2995 3000 3005

Thr Gln His Gln Phe Gly Met Asp Leu Leu Gly Asp Val Gln Ile 3010 3015 3020

Ser Cys Tyr His Ile Leu Cys Ser Leu Tyr Ser Leu Gly Thr Gly Lys 3025 3030 3035 3040

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Ser Leu Ala Ala Ala Ile Pro Val Ala Phe Leu Glu Pro Thr Leu Asn 3060 3065 3070

Arg Tyr Asn Pro Leu Ser Val Phe Asn Thr Lys Thr Pro Arg Glu Arg 3075 3080 3085

Ser Ile Leu Gly Met Pro Asp Thr Val Glu Asp Met Cys Pro Asp Ile 3090 3095 3100

Pro Gln Leu Glu Gly Leu Met Lys Glu Ile Asn Asp Leu Ala Glu Ser 3105 3110 3115 3120

Gly Ala Arg Tyr Thr Glu Met Pro His Val Ile Glu Val Ile Leu Pro 3125 3130 3135

Met Leu Cys Asn Tyr Leu Ser Tyr Trp Trp Glu Arg Gly Pro Glu Asn 3140 3145 3150

Leu Pro Pro Ser Thr Gly Pro Cys Cys Thr Lys Val Thr Ser Glu His 3155 3160 : 3165

Leu Ser Leu Ile Leu Gly Asn Ile Leu Lys Ile Ile Asn Asn Asn Leu 3170 3175 3180

Gly Ile Asp Glu Ala Ser Trp Met Lys Arg Ile Ala Val Tyr Ala Gln 3185 3190 3195 3200

Pro Ile Ile Ser Lys Ala Arg Pro Asp Leu Leu Arg Ser His Phe Ile 3205 3210 3215

Pro Thr Leu Glu Lys Leu Lys Lys Lys Ala Val Lys Thr Val Gln Glu 3220 3225 3230

Glu Glu Gln Leu Lys Ala Asp Gly Lys Gly Asp Thr Gln Glu Ala Glu 3235 3240 3245

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- Gln Asn Phe Val Ile Gln Asn Glu Ile Asn Asn Leu Ala Phe Leu Thr 3315 3320 3325
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- Cys Thr Pro Gly Asp Gln Glu Leu Ile Ser Leu Ala Lys Ser Arg Tyr 3380 3385 3390
- Ser His Arg Asp Thr Asp Glu Glu Val Arg Glu His Leu Arg Asn Asn 3395 3400 3405
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- Asn Leu Tyr Lys Asp Val Leu Lys Ser Glu Glu Pro Phe Asn Pro Glu 3425 3430 3435 3440
- Lys Thr Val Glu Arg Val Gln Arg Ile Ser Ala Ala Val Phe His Leu 3445 3450 3455
- Glu Gln Val Glu Gln Pro Leu Arg Ser Lys Lys Ala Val Trp His Lys 3460 3465 3470
- Leu Leu Ser Lys Gln Arg Lys Arg Ala Val Val Ala Cys Phe Arg Met 3475 3480 3485
- Ala Pro Leu Tyr Asn Leu Pro Arg His Arg Ser Ile Asn Leu Phe Leu 3490 3495 3500
- His Gly Tyr Gln Arg Phe Trp Île Glu Thr Glu Glu Tyr Ser Phe Glu 3505 3510 3515 3520
- Glu Lys Leu Val Gln Asp Leu Ala Lys Ser Pro Lys Val Glu Glu Glu 3525 3530 3535
- Glu Glu Glu Glu Thr Glu Lys Gln Pro Asp Pro Leu His Gln Ile Ile 3540 3550
- Leu Tyr Phe Ser Arg Asn Ala Leu Thr Glu Arg Ser Lys Leu Glu Asp 3555 3565
- Asp Pro Leu Tyr Thr Ser Tyr Ser Ser Met Met Ala Lys Ser Cys Gln 3570 3580
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Tyr Leu Lys Glu Lys Lys Asp Ala Gly Phe Phe Gln Ser Leu Xaa Gly 3665 3670 3680

Leu Met Gln Ser Cys Ser Val Leu Asp Leu Asn Ala Xaa Glu Arg Gln 3685 3690 3695

Asn Lys Ala Glu Gly Leu Gly Met Val Thr Glu Glu Gly Thr Leu Ile 3700 3705 3710

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Gly Gln His Asn Phe Ser Lys Ala Leu Ala Val Thr Lys Gln Ile Phe 3795 3800 3805

Asn Ser Leu Thr Glu Tyr Ile Gln Gly Pro Cys Ile Gly Asn Gln Gln 3810 3820

Ser Leu Ala His Ser Arg Leu Trp Asp Ala Val Val Gly Phe Leu His 3825 3830 3835 . 3840

Val Phe Ala Asn Met Gln Met Lys Leu Ser Gln Asp Ser Ser Gln Ile 3845 3850 3855

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- Val Phe Gly Gly Gly Leu Val Glu Gly Ala Lys Asn Ile Arg Val Thr 4210 4215 4220
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- Asp Thr Met Glu Ala Glu Arg Ala Glu Val Met Glu Pro Gly Ile Thr 4245 4250 4255

- Thr Glu Leu Val His Phe Ile Lys Gly Glu Lys Gly Asp Thr Asp Ile 4260 4265 4270
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- Phe Ala Ile Asn Phe Ile Leu Leu Phe Tyr Lys Val Thr Glu Glu Pro 4420 4425 4430
- Leu Glu Glu Glu Thr Glu Asp Val Ala Asn Leu Trp Asn Ser Phe Asn 4435 4440 4445
- Asp Glu Glu Glu Glu Glu Ala Met Val Phe Phe Val Leu Gln Glu Ser 4450 4455 4460
- Thr Gly Tyr Met Ala Pro Thr Leu Arg Ala Leu Ala Ile Ile His Thr 4465 4470 4475 4480
- Ile Ile Ser Leu Val Cys Val Val Gly Tyr Tyr Cys Leu Lys Val Pro
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- Leu Val Val Phe Lys Arg Glu Lys Glu Ile Ala Arg Lys Leu Glu Phe 4500 4505 4510
- Asp Gly Leu Tyr Ile Thr Glu Gln Pro Ser Glu Asp Asp Ile Lys Gly 4515 4520 4525
- Gln Trp Asp Xaa Leu Val Ile Asn Thr Pro Ser Phe Pro Asn Asn Tyr 4530 4540
- Trp Asp Lys Phe Val Lys Arg Lys Val Ile Asn Lys Tyr Gly Asp Leu 4545 4550 4560
- Tyr Gly Ala Glu Arg Ile Ala Glu Leu Leu Gly Leu Asp Lys Asn Ala 4565 4570 4575

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- Gly Val Val Phe Thr Asp Asn Ser Phe Leu Tyr Leu Ala Trp Tyr Thr 4610 4615 4620
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<212> PRT

<213> Homo sapiens

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- Glu Glu Glu Thr Lys Cys Xaa Glu Leu Leu Arg Ser Gln Thr Glu Lys
 35 40 45
- His Lys Ala Cys Ser Gly Val Trp Asp Asn Ile Thr Cys Trp Arg Pro 50 55 60

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Asn	Phe	Tyr	Ser	Lys 85	Ala	Gly	Asn	Ile	Ser 90		Asn	Cys	Thr	Ser 95	Asp
Gly	Trp	Ser	Glu 100	Thr	Phe	Pro	Asp	Phe 105	Val	Asp	Ala	Cys	Gly 110	_	Ser
Asp	Pro	Glu 115	Asp	Glu	Ser	Lys	11e 120	Thr	Phe	Tyr	Ile	Leu 125	Val	Lys	Ala
Ile	Tyr 130	Thr	Leu	Gly	Tyr	Ser 135	Val	Ser	Leu	Met	Ser 140	Leu	Ala	Thr	Gly
Ser 1 4 5	Ile	Ile	Leu	Cys	Leu 150	Phe	Arg	Lys	Leu	His 155	Cys	Thr	Arg	Asn	Tyr 160
Ile	His	Leu	Asn	Leu 165	Phe	Leu	Ser	Phe	Ile 170	Leu	Arg	Ala	Ile	Ser 175	Val
Leu	Val	Lys	Asp 180	Asp	Val	Leu	Tyr	Ser 185	Ser	Ser	Gly	Thr	Leu 190	His	Cys
Pro	Asp	Gln 195	Pro	Ser	Ser	Trp	Val 200	Gly	Суѕ	Lys	Leu	Ser 205	Leu	Val	Phe
Leu	Gln 210	Tyr	Cys	Ile	Met	Ala 215	Asn	Phe	Phe	Trp	Leu 220	Leu	Val	Glu	Gly
Leu 225	Tyr	Leu	His	Thr	Leu 230	Leu	Val	Ala	Met	Leu 235	Pro	Pro	Arg	Arg	Cys 240
Phe	Leu	Ala	Tyr	Leu 245	Leu	Ile	Gly	Trp	Gly 250	Leu	Pro	Thr	Val	Cys 255	Ile
Gly	Ala	Trp	Thr 260	Ala	Ala	Arg	Leu	Tyr 265	Leu	Glu	Asp	Thr	Gly 270	Cys	Trp
Asp	Thr	Asn 275	Asp	His	Ser	Val	Pro 280	Trp	Trp	Val	Ile	Arg 285	Ile	Pro	Ile
Leu	Ile 290	Ser	Ile	Ile	Val	Asn 295	Phe	Val	Leu	Phe	Ile 300	Ser	Ile	Ile	Arg
Ile 305	Leu	Leu	Gln	Lys	Leu 310	Thr	Ser	Pro	Asp	Val 315	Gly	Gly	Asn	Asp	Gln 320
Ser	Gln	Tyr		Arg 325	Leu	Ala	Lys	Ser	Thr 330	Leu	Leu	Leu	Ile	Pro 335	Leu
Phe	Gly	Val	His 340	Tyr	Met	Val	Phe	Ala 345	Val	Phe	Pro	Ile	Ser 350	Ile	Ser
Ser	Lys	Tyr 355	Gln	Ile	Leu	Phe	Glu 360	Leu	Cys	Leu	Gly	Ser 365	Phe	Gln	Val
Gly	Val 370	Arg	Arg	Arg	Pro							•	٠		

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<400> 128

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Met Cys Leu Glu Lys Ile Gln Arg Ala Asn Glu Leu Met Gly Phe Asn 35 40 45

Asp Ser Ser Pro Gly Cys Pro Gly Met Trp Asp Asn Ile Thr Cys Trp 50 55 60

Lys Pro Ala His Val Gly Glu Met Val Leu Val Ser Cys Pro Glu Leu 65 70 75 80

Phe Arg Ile Phe Asn Pro Asp Gln Asp Met Gly Val Val Ser Arg Asn 85 90 95

Cys Thr Glu Asp Gly Trp Ser Glu Pro Phe Pro His Tyr Phe Asp Ala 100 105 110

Cys Gly Phe Asp Glu Tyr Glu Ser Glu Thr Gly Asp Gln Asp Tyr Tyr 115 120 125

Tyr Leu Ser Val Lys Ala Leu Tyr Thr Val Gly Tyr Ser Thr Ser Leu 130 135 140

Val Thr Leu Thr Thr Ala Met Val Ile Leu Cys Arg Phe Arg Lys Leu 145 150 155 160

His Cys Thr Arg Asn Phe Ile His Met Asn Leu Phe Val Ser Phe Met 165 170 175

Leu Arg Ala Ile Ser Val Phe Ile Lys Asp Trp Ile Leu Tyr Ala Glu 180 185 190

Gln Asp Ser Asn His Cys Phe Ile Ser Thr Val Glu Cys Lys Ala Val 195 200 205

Met Val Phe Phe His Tyr Cys Val Val Ser Asn Tyr Phe Trp Leu Phe 210 215 220

Ile Glu Gly Leu Tyr Leu Phe Thr Leu Leu Val Glu Thr Phe Phe Pro 225 230 235 240

Glu Arg Arg Tyr Phe Tyr Trp Tyr Thr Ile Ile Gly Trp Gly Thr Pro
245 250 255

Thr Val Cys Val Thr Val Trp Ala Thr Leu Arg Leu Tyr Phe Asp Asp 260 265 270

Thr Gly Cys Trp Asp Met Asn Asp Ser Thr Ala Leu Trp Trp Val Ile 275 280 285 290 295 300

Gly Ile Ile Val Ile Leu Val Gln Lys Leu Gln Ser Pro Asp Met Gly 305 310 315 320

Gly Asn Glu Ser Ser Ile Tyr Leu Arg Leu Ala Arg Ser Thr Leu Leu 325 330 335

Leu Ile Pro Leu Phe Gly Ile His Tyr Thr Val Phe Ala Phe Ser Pro 340 345 350

Glu Asn Val Ser Lys Arg Glu Arg Leu Val Phe Glu Leu Gly Leu Gly 355 360 365

Ser Phe Gln Gly Phe Val Val Ala Val Leu Tyr Cys Phe Leu Asn Gly 370 375 380

Glu Val Gln Ala Glu Ile Lys Arg Lys Trp Arg Ser Trp Lys Val Asn 385 390 395 400

Arg Tyr Phe Ala Val Asp Phe Lys His Arg His Pro Ser Leu Ala Ser 405 410 415

Ser Gly Val Asn Gly Gly Thr Gln Leu Ser Ile Leu Ser Lys Ser Ser 420 425 430

Ser Gln Ile Arg Met Ser Gly Leu Pro Ala Asp Asn Leu Ala Thr 435 440 445

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<213> Homo sapiens

<400> 129

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Ala Pro Ala Gly Ala Phe Arg Asn Asp Lys Cys Gly Asp Thr Ile Lys 20 25 30

Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr 35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr
50 55 60

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn 85 90 95

Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val 100 105 110

Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu 115 120 125

	130					135				•	140				
Pro 145	Glu	Cys	Ser	Gln	Asn 150	Tyr	Thr	Thr	Pro	Ser 155	Gly	Val	Ile	Lys	Ser 160
Pro	Gly	Phe	Pro	Glu 165	Lys	Tyr	Pro	Asn	Ser 170	Leu	Glu	Cys	Thr	Tyr 175	Ile
Val	Phe	Ala	Pro 180	Lys	Met	Ser	Glu	Ile 185	Ile	Leu	Glu	Phe	Glu 190	Ser	Phe
Asp	Leu	Glu 195	Pro	Asp	Ser	Asn	Pro 200	Pro	Gly	Gly	Met	Phe 205	Cys	Arg	Tyr
Asp	Arg 210	Leu	Glu	Ile	Trp	Asp 215	Gly	Phe	Pro	Asp	Val 220	Gly	Pro	His	Ile
Gly 225	Arg	Tyr	Cys	Gly	Gln 230	Lys	Thr	Pro	Gly	Arg 235	Ile	Arg	Ser	Ser	Ser 240
Gly	Ile	Leu	Ser	Met 245	Val	Phe	Tyr	Thr	Asp 250	Ser	Ala	Ile	Ala	Lys 255	Glu
Gly	Phe	Ser	Ala 260	Asn	Tyr	Ser	Val	Leu 265	Gln	Ser	Ser	Val	Ser 270	Glu	Asp
Phe	Lys	Cys 275	Met	Glu	Ala	Leu	Gly 280	Met	Glu	Ser	Gly	Glu 285	Ile	His	Ser
Asp	Gln 290	Ile	Thr	Ala	Ser	Ser 295	Gln	Tyr	Ser	Thr	Asn 300	Trp	Ser	Ala	Glu
Arg 305	Ser	Arg	Leu	Asn	Tyr 310	Pro	Glu	Asn	Gly	Trp 315	Thr	Pro	Gly	Glu	Asp 320
Ser	Tyr	Arg	Glu	Trp 325	Ile	Gln	Val	Asp	Leu 330	Gly	Leu	Leu	Arg	Phe 335	Val
Thr	Ala	Val	Gly 340		Gln	Gly	Ala	Ile 345		Lys	Glu	Thr	Lys 350	Lys	Lys
Tyr	Tyr	Val 355	Lys	Thr	Tyr	Lys	Ile 360	Asp	Val	Ser	Ser	Asn 365	Gly	Glu	Asp
Trp	Ile 370		Ile	Lys	Glu	Gly 375	Asn	Lys	Pro	Val	Val 380	Ser			
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			Gly	Leu 5		Leu	Leu	Cys	Ala 10		Leu	Ala	Leu	Val 15	Leu
Ala	Pro	Ala	Gly 20		Phe	Arg	Asn	Asp 25		Cys	Gly	Asp	Thr 30		Lys

35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr 50 55 60

PCT/IL00/00766

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg 65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn 85 90 95

Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val

Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu
115 120 125

Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly 130 135 140

Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser 145

Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile 165 170 175

Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr 195 200 205

Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile
210 215 220

Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser 225 230 235 240

Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu 245 250 255

Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp 260 265 270

Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser 275 280 285

Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu 290 295 300

Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp 305 310 315 320

Ser Tyr Arg Glu Trp Ile Gln Val Cys Ser Ile Arg Ser Ser Leu Ser 325 330 335

Arg Ile Glu

PCT/IL00/00766

<211> 1350 <212> PRT

<213> Homo sapiens

<400> 131

Met Gly Arg Val Gly Tyr Trp Thr Leu Leu Val Leu Pro Ala Leu Leu $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Val Trp Arg Gly Pro Ala Pro Ser Ala Ala Ala Glu Lys Gly Pro Pro 20 25 30

Ala Leu Asn Ile Ala Val Met Leu Gly His Ser His Asp Val Thr Glu 35 40 45

Arg Glu Leu Arg Thr Leu Trp Gly Pro Glu Gln Ala Ala Gly Leu Pro
50 55 60

Leu Asp Val Asn Val Val Ala Leu Leu Met Asn Arg Thr Asp Pro Lys 65 70 75 80

Ser Leu Ile Thr His Val Cys Asp Leu Met Ser Gly Ala Arg Ile His 85 90 95

Gly Leu Val Phe Gly Asp Asp Thr Asp Gln Glu Ala Val Ala Gln Met 100 105 110

Leu Asp Phe Ile Ser Ser His Thr Phe Val Pro Ile Leu Gly Ile His
115 120 125

Gly Gly Ala Ser Met Ile Met Ala Asp Lys Asp Pro Thr Ser Thr Phe 130 135 140

Phe Gln Phe Gly Ala Ser Ile Gln Gln Gln Ala Thr Val Met Leu Lys 145 150 155 160

Ile Met Gln Asp Tyr Asp Trp His Val Phe Ser Leu Val Thr Thr Ile 165 170 175

Phe Pro Gly Tyr Arg Glu Phe Ile Ser Phe Val Lys Thr Thr Val Asp 180 185 190

Asn Ser Phe Val Gly Trp Asp Met Gln Asn Val Ile Thr Leu Asp Thr 195 200 205

Ser Phe Glu Asp Ala Lys Thr Gln Val Gln Leu Lys Lys Ile His Ser 210 215 220

Ser Val Ile Leu Leu Tyr Cys Ser Lys Asp Glu Ala Val Leu Ile Leu 225 230 235 240

Ser Glu Ala Arg Ser Leu Gly Leu Thr Gly Tyr Asp Phe Phe Trp Ile
245
250
255

Val Pro Ser Leu Val Ser Gly Asn Thr Glu Leu Ile Pro Lys Glu Phe 260 265 270

Pro Ser Gly Leu Ile Ser Val Ser Tyr Asp Asp Trp Asp Tyr Ser Leu 275 280 285

Glu Ala Arg Val Arg Asp Gly Ile Gly Ile Leu Thr Thr Ala Ala Ser

Ser 305	Met	Leu	Glu	Lys	Phe 310	Ser	Tyr	Ile	Pro	Glu 315	Ala	Lys	Ala	Ser	Cys 320
Tyr	Gly	Gln	Met	Glu 325	Arg	Pro	Glu	Val	Pro 330	Met	His	Thr	Leu	His 335	Pro
Phe	Met	Val	Asn 340	Val	Thr	Trp	Asp	Gly 345	Lys	Asp	Leu	Ser	Phe 350	Thr	Glu
Glu	Gly	Tyr 355	Gln	Val	His	Pro	Arg 360	Leu	Val	Val	Ile	Val 365	Leu	Asn	Lys
Asp	Arg 370	Glu	Trp	Glu	Lys	Val 375	Gly	Lys	Tṛp	Glu	Asn 380	His	Thr	Leu	Ser
Leu 385	Arg	His	Ala	Val	Trp 390	Pro	Arg	Tyr	Lys	Ser 395	Phe	Ser	Asp	Cys	Glu 400
Pro	Asp	Asp	Asn	His 405	Leu	Ser	Ile	Val	Thr 410	Leu	Glu	Glu	Ala	Pro 415	Phe
Val	Ile	Val	Glu 420	Asp	Ile	Asp	Pro	Leu 425	Thr	Glu	Thr	Cys	Val 430	Arg	Asn
Thr	Val	Pro 435	Cys	Arg	Lys	Phe	Val 440	Lys	Ile	Asn	Asn	Ser 445	Thr	Asn	Glu
Gly	Met 450	Asn	Val	Lys	Lys	Cys 455	Cys	Lys	Gly	Phe	Cys 460	Ile	Asp	Ile	Leu
Lys 465	Lys	Leu	Ser	Arg	Thr 470	Val	Lys	Phe	Thr	Tyr 475	Asp	Leu	Tyr	Leu	Val 480
Thr	Asn	Gly	Lys	His 485	Gly	Lys	Lys	Val	Asn 490	Asn	Val	Trp	Asn	Gly 495	Met
		-	Lys Val 500	485		-	-		490			•		495	
Ile	Gly	Glu	Val	485 Val	Tyr	Gln	Arg	Ala 505	490 Val	Met	Ala	Val	Gly 510	495 Ser	Leu
Ile Thr	Gly	Glu Asn 515	Val 500	485 Val Glu	Tyr Arg	Gln	Arg Glu 520	Ala 505 Val	490 Val ; Val	Met Asp	Ala Phe	Val Ser 525	Gly 510 Val	495 Ser Pro	Leu Phe
Ile Thr Val	Gly Ile Glu 530	Glu Asn 515 Thr	Val 500 Glu	485 Val Glu Ile	Tyr Arg Ser	Gln Ser Val 535	Arg Glu 520 Met	Ala 505 Val Val	490 Val ; Val Ser	Met Asp Arg	Ala Phe Ser 540	Val Ser 525 Asn	Gly 510 Val	495 Ser Pro	Leu Phe Val
Thr Val Ser 545	Gly Ile Glu 530 Pro	Glu Asn 515 Thr	Val 500 Glu Gly	485 Val Glu Ile Phe	Tyr Arg Ser Leu 550	Gln Ser Val 535 Glu	Arg Glu 520 Met	Ala 505 Val Val	490 Val ; Val Ser	Met Asp Arg Ala 555	Ala Phe Ser 540 Ser	Val Ser 525 Asn Val	Gly 510 Val Gly	495 Ser Pro Thr	Leu Phe Val Met 560
Thr Val Ser 545 Met	Gly Ile Glu 530 Pro	Glu Asn 515 Thr Ser	Val 500 Glu Gly	485 Val Glu Ile Phe Leu 565	Tyr Arg Ser Leu 550	Gln Ser Val 535 Glu	Arg Glu 520 Met Pro	Ala 505 Val Val Phe Ser	490 Val ; Val Ser Ser Ala 570	Met Asp Arg Ala 555	Ala Phe Ser 540 Ser	Val Ser 525 Asn Val	Gly 510 Val Gly Trp	495 Ser Pro Thr Val Val 575	Leu Phe Val Met 560 Phe
Thr Val Ser 545 Met	Gly Ile Glu 530 Pro Phe	Glu Asn 515 Thr Ser Val	Val 5000 Glu Gly Ala Met	485 Val Glu Ile Phe Leu 565 Pro	Tyr Arg Ser Leu 550 Leu Val	Gln Ser Val 535 Glu Ile	Arg Glu 520 Met Pro Val	Ala 505 Val Val Phe Ser Asn 585	490 Val ; Val Ser Ser Ala 570 Arg	Met Asp Arg Ala 555 Ile Asn	Ala Phe Ser 540 Ser Ala Leu	Val Ser 525 Asn Val Val	Gly 510 Val Gly Trp Phe Lys 590	495 Ser Pro Thr Val Val 575 Gly	Leu Phe Val Met 560 Phe

Th: 625	Thr	: Sei	r Lys	5 Il€	e Met 630	. Val	. Ser	Val	Trp	Ala 635		Ph	e Al	a Va	1 Ile 640
Ph∈	e Leu	ı Alá	a Ser	Tyr 645	Thr	Ala	Asn	Leu	Ala 650	a Ala	a Phe	e Me	t Il	e Gl: 65:	n Glu 5
Glu	Phe	e Val	Asp 660	Glr	val	Thr	Gly	Leu 665	Ser	· Asp	Lys	Lys	5 Phe 670		n Arg
Pro	His	675	Tyr	Ser	Pro	Pro	Phe 680	Arg	Phe	Gly	Thr	Va]		o Ası	n Gly
Ser	Thr 690	Glu	Arg	Asn	Ile	Arg 695	Asn	Asn	Tyr	Pro	700	Met	His	s Glr	Tyr
Met 705	Thr	Lys	Phe	Asn	Gln 710	Lys	Gly	Val	Glu	Asp 715	Ala	Leu	ı Val	. Ser	Leu 720
				725					730					735	
			/40					745		•			750	•	Ser
		/55					760					765			Gly
	770					775					780				Gly
785					790					795					Cys 800
				805					810					815	Asn
			Val 820					825					830		
		833					840					845			Cys
	850		Val			855					860				
865			Tyr		870					875					880
			Asp	885			•		890					895	
			Ser 900					905					910		
		915	Asp				920					925			
	930		Met			935					940				
asp	ASN	Arg	Ser	rue	GIN	GIA	Lys (Glu .	Ser	Ile	Phe	Gly	Asp	Asn	Met

Asn Glu Leu Gln Thr Phe Val Ala Asn Arg Gln Lys Asp Asn Leu Asn 965 970 975

Asn Tyr Val Phe Gln Gly Gln His Pro Leu Thr Leu Asn Glu Ser Asn 980 985 990

Pro Asn Thr Val Glu Val Ala Val Ser Thr Glu Ser Lys Ala Asn Ser 995 1000 1005

Arg Pro Arg Gln Leu Trp Lys Lys Ser Val Asp Ser Ile Arg Gln Asp 1010 1015 1020

Ser Leu Ser Gln Asn Pro Val Ser Gln Arg Asp Glu Ala Thr Ala Glu 1025 1030 1035 1040

Asn Arg Thr His Ser Leu Lys Ser Pro Arg Tyr Leu Pro Glu Glu Met 1045 1050 1055

Ala His Ser Asp Ile Ser Glu Thr Ser Asn Arg Ala Thr Cys His Arg 1060 1065 1070

Glu Pro Asp Asn Ser Lys Asn His Lys Thr Lys Asp Asn Phe Lys Arg 1075 1080 1085

Ser Val Ala Ser Lys Tyr Pro Lys Asp Cys Ser Glu Val Glu Arg Thr 1090 1095 1100

Tyr Leu Lys Thr Lys Ser Ser Ser Pro Arg Asp Lys Ile Tyr Thr Ile 1105 1110 1115 1120

Asp Gly Glu Lys Glu Pro Gly Phe His Leu Asp Pro Pro Gln Phe Val

Glu Asn Val Thr Leu Pro Glu Asn Val Asp Phe Pro Asp Pro Tyr Gln 1140 1150

Asp Pro Ser Glu Asn Phe Arg Lys Gly Asp Ser Thr Leu Pro Met Asn 1155 1160 1165

Arg Asn Pro Leu His Asn Glu Glu Gly Leu Ser Asn Asn Asp Gln Tyr 1170 1175 1180

Lys Leu Tyr Ser Lys His Phe Thr Leu Lys Asp Lys Gly Ser Pro His 1185 1190 1195 1200

Ser Glu Thr Ser Glu Arg Tyr Arg Gln Asn Ser Thr His Cys Arg Ser 1205 1210 1215

Cys Leu Ser Asn Met Pro Thr Tyr Ser Gly His Phe Thr Met Arg Ser 1220 1225 1230

Pro Phe Lys Cys Asp Ala Cys Leu Arg Met Gly Asn Leu Tyr Asp Ile 1235 1240 1245

Asp Glu Asp Gln Met Leu Gln Glu Thr Arg Asp Asp Gln Arg Leu Val 1250 1255 1260

Ile Gly Arg Cys Pro Ser Asp Pro Tyr Lys His Ser Leu Pro Ser Gln 1265 1270 1275 1280

Ala Val Asn Asp Ser Tyr Leu Arg Ser Ser Leu Arg Ser Thr Ala Ser 1290 Tyr Cys Ser Arg Asp Ser Arg Gly His Asn Asp Val Tyr Ile Ser Glu 1305 His Val Met Pro Tyr Ala Ala Asn Lys Asn Asn Met Tyr Ser Thr Pro 1320 Arg Val Leu Asn Ser Cys Ser Asn Arg Arg Val Tyr Lys Lys Met Pro Ser Ile Glu Ser Asp Val <210> 132 <211> 455 <212> PRT <213> Homo sapiens <400> 132 Met Arq Thr Leu Leu Pro Pro Ala Leu Leu Thr Cys Trp Leu Leu Ala 5 Pro Val Asn Ser Ile His Pro Glu Cys Arg Phe His Leu Glu Ile Gln Glu Glu Glu Thr Lys Cys Xaa Glu Leu Leu Arg Ser Gln Thr Glu Lys His Lys Ala Cys Ser Gly Val Trp Asp Asn Ile Thr Cys Trp Arg Pro Ala Asn Val Gly Glu Thr Val Thr Val Pro Cys Pro Lys Val Phe Ser Asn Phe Tyr Ser Lys Ala Gly Asn Ile Ser Lys Asn Cys Thr Ser Asp Gly Trp Ser Glu Thr Phe Pro Asp Phe Val Asp Ala Cys Gly Tyr Ser Asp Pro Glu Asp Glu Ser Lys Ile Thr Phe Tyr Ile Leu Val Lys Ala 120 Ile Tyr Thr Leu Gly Tyr Ser Val Ser Leu Met Ser Leu Ala Thr Gly 135 Ser Ile Ile Leu Cys Leu Phe Arg Lys Leu His Cys Thr Arg Asn Tyr 150 155 Ile His Leu Asn Leu Phe Leu Ser Phe Ile Leu Arg Ala Ile Ser Val 170 165 Leu Val Lys Asp Asp Val Leu Tyr Ser Ser Ser Gly Thr Leu His Cys Pro Asp Gln Pro Ser Ser Trp Val Gly Cys Lys Leu Ser Leu Val Phe

Leu Gln Tyr Cys Ile Met Ala Asn Phe Phe Trp Leu Leu Val Glu Gly 210 215 Leu Tyr Leu His Thr Leu Leu Val Ala Met Leu Pro Pro Arg Arg Cys 235 230 Phe Leu Ala Tyr Leu Leu Ile Gly Trp Gly Leu Pro Thr Val Cys Ile 250 245 Gly Ala Trp Thr Ala Ala Arg Leu Tyr Leu Glu Asp Thr Gly Cys Trp 260 Asp Thr Asn Asp His Ser Val Pro Trp Trp Val Ile Arg Ile Pro Ile 280 Leu Ile Ser Ile Ile Val Asn Phe Val Leu Phe Ile Ser Ile Ile Arg 295 Ile Leu Leu Gln Lys Leu Thr Ser Pro Asp Val Gly Gly Asn Asp Gln 315 Ser Gln Tyr Lys Arg Leu Ala Lys Ser Thr Leu Leu Leu Ile Pro Leu 330 Phe Gly Val His Tyr Met Val Phe Ala Val Phe Pro Ile Ser Ile Ser 345 340 Ser Lys Tyr Gln Ile Leu Phe Glu Leu Cys Leu Gly Ser Phe Gln Gly 360 Leu Val Val Ala Val Leu Tyr Cys Phe Leu Asn Ser Glu Val Ser Ser 380 375 Trp Pro Pro Trp Asn Gln Ala Gln Val Leu Thr Cys Phe Leu Arg Cys 395 390 385 Cys Pro Ala Trp Cys Arg Ser Pro His Thr Cys Leu Ser Ser Ala Gly 410 405 Ser Ser Tyr Cys Pro Gly Pro His Ser Ser Val Ser Pro Ser Glu Asn 420 Pro Gln Arg His Arg Gln Thr His Ser Ser Gly Pro Ser Phe Gln Thr 440 435 Pro Pro Ser Phe Arg Pro Pro <210> 133 <211> 452 <212> PRT <213> Homo sapiens <400> 133 Met Arg Thr Leu Leu Pro Pro Ala Leu Leu Thr Cys Trp Leu Leu Ala 10 Pro Val Asn Ser Ile His Pro Glu Cys Arg Phe His Leu Glu Ile Gln 25

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His	Lys 50	Ala	Cys	Ser	Gly	Val 55	Trp	Asp	Asn	Ile	Thr 60	Cys	Trp	Arg	Pro
Ala 65	Asn	Val	Gly	Glu	Thr 70	Val	Thr	Val	Pro	Cys 75	Pro	Lys	Val	Phe	Ser 80
Asn	Phe	Tyr	Ser	Lys 85	Ala	Gly	Asn	Ile	Ser 90	Lys	Asn	Cys	Thr	Ser .95	Asp
Gly	Trp	Ser	Glu 100	Thr	Phe	Pro	Asp	Phe 105	Val	Asp	Ala	Cys	Gly 110	Tyr	Ser
Asp	Pro	Glu 115	Asp	Glu	Ser	Lys	Ile 120	Thr	Phe	Tyr	Ile	Leu 125		Lys	Ala
Ile	Tyr 130	Thr	Leu	Gly	Tyr	Ser 135	Val	Ser	Leu	Met	Ser 140	Leu	Ala	Thr	Gly
Ser 145	Ile	Ile	Leu	Cys	Leu 150	Phe	Arg	Lys	Leu	His 155	Cys	Thr	Arg	Asn	Tyr 160
Ile	His	Leu	Asn	Leu 165	Phe	Leu	Ser	Phe	Ile 170	Leu	Arg	Ala	Ile	Ser 175	Val
Leu	Val	Lys	Asp 180	Asp	Val	Leu	Tyr	Ser 185	Ser	Ser	Gly	Thr	Leu 190	His	Cys
Pro	Asp	Gln 195	Pro	Ser	Ser	Trp	Val 200	Gly	Cys	Lys	Leu	Ser 205	Leu	Val	Phe
Leu	Gln 210	Tyr	Cys	Ile	Met	Ala 215	Asn	Phe	Phe	Trp	Leu 220	Leu	Val	Glu	Gly
Leu 225	Tyr	Leu	His	Thr	Leu 230	Leu	Val	Ala	Met	Leu 235	Pro	Pro	Arg	Arg	Cys 240
Phe	Leu	Ala	Tyr	Leu 245	Leu	Ile	Gly	Trp	Gly 250	Leu	Pro	Thr	Val	Cys 255	Ile
Gly	Ala	Trp	Thr 260	Ala	Ala	Arg	Leu	Tyr 265	Leu	Glu	Asp	Thr	Gly 270	Суѕ	Trp
Asp	Thr	Asn 275	Asp	His	Ser	Val	Pro 280	Trp	Trp	Val	Ile	Arg 285	Ile	Pro	Ile
Leu	Ile 290	Ser	Ile	Ile	Val	Asn 295	Phe	Val	Leu	Phe	Ile 300	Ser	Ile	Ile	Arg
Ile 305		Leu	Gln	Lys	Leu 310	Thr	Ser	Pro	Asp	Val 315	Gly	Gly	Asn	Asp	Gln 320
Ser		Tur	Lvs	Ara	Leu	Ala	Lys	Ser	Thr	Leu	Leu	Leu	Ile	Pro	Leu
	Gin	1 7 1	-,-	325					330					335	

Ser Lys Tyr Gln Ile Leu Phe Glu Leu Cys Leu Gly Ser Phe Gln Gly 360 Leu Val Val Ala Val Leu Tyr Cys Phe Leu Asn Ser Glu Val Ser Ser 375 Trp Pro Pro Trp Asn Gln Ala Gln Val Leu Thr Cys Phe Leu Arg Cys Cys Pro Ala Trp Cys Arg Ser Pro His Thr Cys Leu Ser Ser Ala Gly 405 410 Ser Ser Tyr Cys Pro Gly Pro His Ser Ser Val Ser Pro Ser Glu Asn 425 Pro Gln Arg His Arg Gln Thr His Ser Ser Gly Trp Gly Val Gly Leu 440 His Ser Val Leu 450 <210> 134 <211> 1344 <212> PRT <213> Homo sapiens <400> 134 Met Lys Ser Gly Ser Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile 25 Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val 70 Ile Thr Glu Tyr Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe 105 Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile 115 Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile 145 150 155 Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys 165 170

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys 220 Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser 235 Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr 250 Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met 295 Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn 360 Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val 375 Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Gly 410 Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp 420 Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr 490 Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr

505 500 510 Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys 520 Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys 535 540 Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys 545 555 Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln 570 Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp 585 His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala 595 Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser 615 Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn 630 635 Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr 650 Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys .675 Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys 695 Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys 705 1 715 Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser 745 Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro 755 Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg 795 Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser 810 Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp 820 825

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile 840 Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met 855 860 Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val 870 875 Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu 885 890 Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly 905 Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr 920 Gly Tyr Glu Asn Phe Ile His Leu Ile Ile Ala Leu Pro Val Ala Val 935 Leu Leu Ile Val Gly Gly Leu Val Ile Met Leu Tyr Val Phe His Arg Lys Arg Asn Asn Ser Arg Leu Gly Asn Gly Val Leu Tyr Ala Ser Val 965 970 Asn Pro Glu Tyr Phe Ser Ala Ala Asp Val Tyr Val Pro Asp Glu Trp 980 Glu Val Ala Arg Glu Lys Ile Thr Met Ser Arg Glu Leu Gly Gln Gly 1000 Ser Phe Gly Met Val Tyr Glu Gly Val Ala Lys Gly Val Val Lys Asp 1015 Glu Pro Glu Thr Arg Val Ala Ile Lys Thr Val Asn Glu Ala Ala Ser 1025 1030 1035 Met Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val Met Lys Glu 1045 1050 Phe Asn Cys His His Val Val Arg Leu Leu Gly Val Val Ser Gln Gly 1060 Gln Pro Thr Leu Val Ile Met Glu Leu Met Thr Arg Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Met Glu Asn Asn Pro Val Leu 1095 Ala Pro Pro Ser Leu Ser Lys Met Ile Gln Met Ala Gly Glu Ile Ala 1105 1110 Asp Gly Met Ala Tyr Leu Asn Ala Asn Lys Phe Val His Arg Asp Leu 1125 1130 Ala Ala Arg Asn Cys Met Val Ala Glu Asp Phe Thr Val Lys Ile Gly

1145

1150

1140

Asp Phe Glv Met Thr Arg Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys 1155 1160 1165

Gly Gly Lys Gly Leu Leu Pro Val Arg Trp Met Ser Pro Glu Ser Leu 1170 1180

Lys Asp Gly Val Phe Thr Thr Tyr Ser Asp Val Trp Ser Phe Gly Val 1185 1190 1195

Val Leu Trp Glu Ile Ala Thr Leu Ala Glu Gln Pro Tyr Gln Gly Leu 1205 1210 1215

Ser Asn Glu Gln Val Leu Arg Phe Val Met Glu Gly Gly Leu Leu Asp 1220 1225 1230

Lys Pro Asp Asn Cys Pro Asp Met Leu Phe Glu Leu Met Arg Met Cys 1235 1240 1245

Trp Gln Tyr Asn Pro Lys Met Arg Pro Ser Phe Leu Glu Ile Ile Ser 1250 1255 1260

Ser Ile Lys Glu Glu Leu Asp Leu Glu Pro Glu Asn Met Glu Ser Val 1265 1270 1275 1280

Pro Leu Asp Pro Ser Ala Ser Ser Ser Ser Leu Pro Leu Pro Asp Arg 1285 1290 1295

His Ser Gly His Lys Ala Glu Asn Gly Pro Gly Pro Gly Val Leu Val 1300 1305 1310

Leu Arg Ala Ser Phe Asp Glu Arg Gln Pro Tyr Ala His Met Asn Gly 1315 1320 1325

Gly Arg Lys Asn Glu Arg Ala Leu Pro Leu Pro Gln Ser Ser Thr Cys 1330 1340

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<210> 135

<211> 600

<212> PRT

<213> Homo sapiens

<400> 135

Met Glu Arg Gly Leu Pro Leu Leu Cys Ala Val Leu Ala Leu Val Leu 1 5 10 15

Ala Pro Ala Gly Ala Phe Arg Asn Asp Lys Cys Gly Asp Thr Ile Lys
20 25 30

Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr
50 55 60

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg 65 70 75 80

Asp	Cys	Lys	Tyr	Asp 85	Tyr	Val	Glu	Val	Phe 90	Asp	Gly	Glu	Asn	Glu 95	Asn
Gly	His	Phe	Arg 100	Gly	Lys	Phe	Cys	Gly 105	Lys	Ile	Ala	Pro	Pro 110	Pro	Val
Val	Ser	Ser 115	Gly	Pro	Phe	Leu	Phe 120	Ile	Lys	Phe	Val	Ser 125	Asp	Tyr	Glu
Thr	His 130	Gly	Ala	Gly	Phe	Ser 135	Ile	Arg	Tyr	Glu	Ile 140	Phe	Lys	Arg	Gly
Pro 145	Glu	Cys	Ser	Gln	Asn 150	Tyr	Thr	Thr	Pro	Ser 155	Gly	Val	Ile	Lys	Ser 160
Pro	Gly	Phe	Pro	Glu 165	Lys	Tyr	Pro	Asn	Ser 170	Leu	Glu	Cys	Thr	Tyr 175	Ile
Val	Phe	Ala	Pro 180	Lys	Met	Ser	Glu	Ile 185	Ile	Leu	Glu	Phe	Glu 190	Ser	Phe
Asp	Leu	Glu 195	Pro	Asp	Ser	Asn	Pro 200	Pro	Gly	Gly	Met	Phe 205	Cys	Arg	Tyr
Asp	Arg 210	Leu	Glu	Ile	Trp	Asp 215	Gly	Phe	Pro	Asp	Val 220	Gly	Pro	His	Ile
Gly 225	Arg	Tyr	Cys	Gly	Gln 230	Lys	Thr	Pro	Gly	Arg 235	Ile	Arg	Ser	Ser	Ser 240
Gly	Ile	Leu	Ser	Met 245	Val	Phe	Tyr	Thr	Asp 250	Ser	Ala	Ile	Ala	Lys 255	Glu
Gly	Phe	Ser	Ala 260	Asn	Tyr	Ser	Val	Leu 265	Gln	Ser	Ser	Val	Ser 270	Glu	Asp
Phe	Lys	Cys 275	Met	Glu	Ala	Leu	Gly 280	Met	Glu	Ser	Gly	Glu 285	Ile	His	Ser
Asp	Gln 290	Ile	Thr	Ala	Ser	Ser 295	Gln	Tyr	Ser	Thr	Asn 300	Trp	Ser	Ala	Glu
Arg 305	Ser	Arg	Leu	Asn	Tyr 310	Pro	Glu	Asn	Gly	Trp 315	Thr	Pro	Gly	Glu	Asp 320
Ser	Tyr	Arg	Glu	Trp 325	Ile	Gln	Val	Asp	Leu 330	Gly	Leu	Leu	Arg	Phe 335	Val
Thr	Ala	Val	Gly 340	Thr	Gln	Gly		11e 345	Ser	Lys	Glu	Thr	Lys 350	Lys	Lys
Tyr	Tyr	Val 355	Lys	Thr	Tyr	Lys	Ile 360	Asp	Val	Ser	Ser	Asn 365	Gly	Glu	Asp
Trp	Ile 370	Thr	Ile	Lys	Glu	Gly 375	Asn	Lys	Pro	Val	Leu 380	Phe	Gln	Gly	Asn
Thr 385	Asn	Pro	Thr	Asp	Val 390	Val	Val	Ala	Val	Phe 395	Pro	Lys	Pro	Leu	Ile 400
Thr	Arg	Phe	Val	Arg	Ile	Lys	Pro	Ala	Thr	Trp	Glu	Thr	Gly	Ile	Ser

410 . 415

Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser 420 425 430

Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr 435 440 445

Ser Ser Asn Gln Gly Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu 450 455 460

Val Thr Ser Arg Ser Gly Trp Ala Leu Pro Pro Ala Pro His Ser Tyr 465 470 475 480

Ile Asn Glu Trp Leu Gln Ile Asp Leu Gly Glu Glu Lys Ile Val Arg
485 490 495

Gly Ile Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met 500 505 510

Arg Lys Phe Lys Ile Gly Tyr Ser Asn Asn Gly Ser Asp Trp Lys Met 515 520 525

Ile Met Asp Asp Ser Lys Arg Lys Ala Lys Ser Phe Glu Gly Asn Asn 530 540

Asn Tyr Asp Thr Pro Glu Leu Arg Thr Phe Pro Ala Leu Ser Thr Arg 545 550 555 560

Phe Ile Arg Ile Tyr Pro Glu Arg Ala Thr His Gly Gly Leu Gly Leu 565 570 575

Arg Met Glu Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro 580 585 590

Thr Thr Pro Asn Gly Asn Leu Val 595 600

<210> 136

<211> 840

<212> PRT

<213> Homo sapiens

<400> 136

Met Glu Arg Gly Leu Pro Leu Leu Cys Ala Val Leu Ala Leu Val Leu 1 5 10 15

Ala Pro Ala Gly Ala Phe Arg Asn Asp Lys Cys Gly Asp Thr Ile Lys
20 25 30

Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr 35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr 50 55 60

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn

85 90 · 95 Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val 105 Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu 120 Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly 130 135 Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser 150 Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile 170 165 Val Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe 185 Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr 200 Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile 215 Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu 250 245 Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu 295 Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp Ser Tyr Arg Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val 330 Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys Tyr Tyr Val Lys Thr Tyr Lys Ile Asp Val Ser Ser Asn Gly Glu Asp Trp Ile Thr Ile Lys Glu Gly Asn Lys Pro Val Leu Phe Gln Gly Asn 375 Thr Asn Pro Thr Asp Val Val Val Ala Val Phe Pro Lys Pro Leu Ile

Thr Arg Phe Val Arg Ile Lys Pro Ala Thr Trp Glu Thr Gly Ile Ser

395

410

390

405

Met	Arg	Phe	Glu 420	Val	Tyr	Gly	Cys	Lys 425	Ile	Thr	Asp	Tyr	Pro 430	Cys	Ser
Gly	Met	Leu 435	Gly	Met	Val	Ser	Gly 440	Leu	Ile	Ser	Asp	Ser 445	Gln	Ile	Thi
Ser	Ser 450	Asn	Gln	Gly	Asp	Arg 455	Asn	Trp	Met	Pro	Glu 460	Asn	Ile	Arg	Leu
Val 465	Thr	Ser	Arg	Ser	Gly 470	Trp	Ala	Leu	Pro	Pro 475	Ala	Pro	His	Ser	Туг 480
Ile	Asn	Glu	Trp	Leu 485	Gln	Ile	Asp	Leu	Gly 490	Glu	Glu	Lys	Ile	Val 495	Arg
			Ile 500					505					510		
Arg	Lys	Phe 515	Lys	Ile	Gly	Tyr	Ser 520	Asn	Asn	Gly	Ser	Asp 525	Trp	Lys	Met
	530		Asp			535	_		_		540				
545			Lys		550					555					560
			Gly	565					570					575	
			Trp 580					585					590		
		595	Lys				600					605	_	_	
	610		Ser			615				_	620				-
625			Pro		630					635					640
			His	645					650					655	_
Leu	Arg	Tyr	Gln 660	Lys	Pro	Glu	Glu	Tyr 665	Asp	Gln	Leu	Val	Trp 670		Ala
		675	Gln				680				_	685			
Lys	Ser 690	Leu	Lys	Leu	Tyr	Gln 695	Val	Ile	Phe	Glu	Gly 700	Glu	Ile	Gly	Lys
705	2 .		Gly		710					715					720
Ile	Ser	Gln	Glu	Asp 725	Cys	Ala	Lys	Pro	Ala 730	Asp	Leu	Asp	Lys	Lys 735	Asn

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ro Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly Tyr Glu Gly
            740
                                745
 lu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly Asn Val Leu
                            760
 ys Thr Leu Xaa Pro Ile Leu Ile Thr Ile Ile Ala Met Ser Ala Leu
3ly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr Cys Ala Cys
                    790
Irp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu Glu Asn Tyr
                                    810
Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp Lys Leu Asn
                               825
Thr Gln Ser Thr Tyr Ser Glu Ala
        835
<210> 137
<211> 538
<212> PRT
<213> Homo sapiens
<400> 137
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Ala Pro Ala Gly Ala Phe Arg Asn Asp Lys Cys Gly Asp Thr Ile Lys
Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr
                             40
His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr
                         55
                                     . .
Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn
Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val
                                105
Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu
                            120
        115
Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly
Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser
                    150
                                        155
Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile
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Val Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe 185 Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu 250 Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser 280 Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu 295 Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp Ser Tyr Arg Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Tyr Tyr Val Lys Thr Tyr Lys Ile Asp Val Ser Ser Asn Gly Glu Asp 360 Trp Ile Thr Ile Lys Glu Gly Asn Lys Pro Val Leu Phe Gln Gly Asn 375 Thr Asn Pro Thr Asp Val Val Val Ala Val Phe Pro Lys Pro Leu Ile Thr Arg Phe Val Arg Ile Lys Pro Ala Thr Trp Glu Thr Gly Ile Ser 410 Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser 420 Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr Ser Ser Asn Gln Gly Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu 455 Val Thr Ser Arg Ser Gly Trp Ala Leu Pro Pro Ala Pro His Ser Tyr 465 Ile Asn Glu Trp Leu Gln Ile Asp Leu Gly Glu Lys Ile Val Arg Gly Ile Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met

500 505 510

Arg Lys Phe Lys Ile Gly Tyr Ser Asn Asn Gly Ser Asp Trp Lys Met 515 520 525

Ile Met Asp Asp Ser Lys Arg Lys Ala Arg 530 535

<210> 138

<211> 389

<212> PRT

<213> Homo sapiens

<400> 138

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile 1 5 10 15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
20 25 30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
35 40 45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro 50 55 60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly 65 70 75 80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val 85 90 95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg 100 105 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala 115 120 125

Pro Ser Ser Gly Asp Asp Glu Asp Glu Asp Glu Ala Glu Asp Thr 130 135 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp 145 150 155 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys 165 170 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly 180 185 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His 195 200 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly 210 215 220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr 225 230 235 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln

245 250 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu 260 265 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu 275 280 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro 290 295 300

Tyr Val Thr Val Leu Lys Ser Trp Ile Ser Glu Ser Val Glu Ala Asp 305 310 315 320

Val Arg Leu Arg Leu Ala Asn Val Ser Glu Arg Asp Gly Glu Tyr 325 330 335

Leu Cys Arg Ala Thr Asn Phe Ile Gly Val Ala Glu Lys Ala Phe Trp 340 345 350

Leu Ser Val His Gly Pro Arg Ala Gly Asn Asp Ser Val Pro Cys Arg 355 360 365

Pro Ala Gln Glu Leu Gln Leu Gln Gly Pro Gly Arg Ala Pro Cys Thr 370 380

Pro Arg Thr Pro Ser 385

<210> 139

<211> 330

<212> PRT

<213> Mouse

<400> 139

Met Thr Leu Arg His Leu Pro Phe Ile Leu Leu Leu Ile Leu Ser Gly
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Glu Leu Tyr Ala Glu Glu Lys Gln Cys Asp Phe Pro Thr Val Glu Asn
20 25 30

Gly Arg Ile Ala Gln Tyr Tyr Tyr Thr Phe Lys Ser Phe Tyr Phe Pro
35 40 45

Met Ser Val Asp Lys Lys Leu Ser Phe Phe Cys Leu Ala Gly Tyr Ala 50 55 60

Thr Glu Ser Gly Lys Gln Glu Glu Gln Ile Arg Cys Thr Ala Glu Gly 65 70 75 80

Trp Ser Pro Asn Pro Arg Cys Tyr Lys Lys Cys Leu Lys Pro Asp Leu
85 90 95

Arg Asn Gly Tyr Val Ser Asn Asp Lys Val Leu Tyr Lys Leu Gln Glu
100 105 110

Arg Met Ser Tyr Gly Cys Ser Ser Gly Tyr Lys Thr Thr Gly Gly Lys
115 120 125

Asp Glu Glu Val Val His Cys Leu Ser Ala Gly Trp Ser Ser Gln Pro

130 135 140 Ser Cys Arg Lys Glu Gln Glu Thr Cys Leu Ala Pro Glu Leu Glu His 150 Gly Asn Tyr Ser Thr Thr Gln Arg Thr Phe Lys Val Lys Asp Ile Val 170 Ala Tyr Thr Cys Thr Ala Gly Tyr Tyr Thr Thr Thr Gly Lys Gln Thr Gly Glu Ala Glu Cys Gln Ala Asn Gly Trp Ser Leu Thr Pro Gln Cys 200 Asn Lys Leu Met Cys Ser Ser Leu Arg Leu Ile Glu Asn Gly Tyr Phe 215 His Pro Val Lys Gln Thr Tyr Glu Glu Gly Asp Val Val Gln Phe Phe 235 Cys His Glu Asn Tyr Tyr Leu Ser Gly Ser Asp Leu Ile Gln Cys Tyr 245 250 Asn Phe Gly Trp Tyr Pro Glu Ser Pro Ile Cys Glu Gly Arg Arg Asn Arg Cys Pro Pro Pro Pro Val Pro Leu Asn Ser Lys Ile Gln Pro His 280 Ser Thr Thr Tyr Arg His Gly Glu Arg Val His Ile Glu Cys Glu Leu 295 Asn Phe Val Ile Gln Gly Ser Glu Glu Leu Leu Cys Glu Asn Gly Lys 310 Trp Thr Glu Pro Pro Lys Cys Ile Gly Trp <210> 140 <211> 1073 <212> PRT <213> Mouse <400> 140 Met Pro Trp Gly Arg Arg Pro Thr Trp Leu Leu Leu Ala Phe Leu Leu Val Phe Leu Lys Ile Ser Ile Leu Ser Val Thr Ala Trp Gln Thr Gly 25 Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser Arg Ile Asp Pro Asp Gly Thr Asn His Gln Gln Leu Val Val Asp Ala

Gly Ile Ser Ala Asp Met Asp Ile His Tyr Lys Lys Glu Arg Leu Tyr

85 90 · 95

Trp Val Asp Val Glu Arg Gln Val Leu Leu Arg Val Phe Leu Asn Gly
100 . 105 110

Thr Gly Leu Glu Lys Val Cys Asn Val Glu Arg Lys Val Ser Gly Leu 115 120 125 .

Ala Ile Asp Trp Ile Asp Asp Glu Val Leu Trp Val Asp Gln Gln Asn 130 135 140

Gly Val Ile Thr Val Thr Asp Met Thr Gly Lys Asn Ser Arg Val Leu 145 150 155 160

Leu Ser Ser Leu Lys His Pro Ser Asn Ile Ala Val Asp Pro Ile Glu 165 170 175

Arg Leu Met Phe Trp Ser Ser Glu Val Thr Gly Ser Leu His Arg Ala 180 185 190

His Leu Lys Gly Val Asp Val Lys Thr Leu Leu Glu Thr Gly Gly Ile 195 200 205

Ser Val Leu Thr Leu Asp Val Leu Asp Lys Arg Leu Phe Trp Val Gln 210 215 220

Asp Ser Gly Glu Gly Ser His Ala Tyr Ile His Ser Cys Asp Tyr Glu 225 230 235 240

Gly Gly Ser Val Arg Leu Ile Arg His Gln Ala Arg His Ser Leu Ser 245 250 255

Ser Met Ala Phe Phe Gly Asp Arg Ile Phe Tyr Ser Val Leu Lys Ser 260 265 270

Lys Ala Ile Trp Ile Ala Asn Lys His Thr Gly Lys Asp Thr Val Arg 275 280 285

Ile Asn Leu His Pro Ser Phe Val Thr Pro Gly Lys Leu Met Val Val 290 295 4 300

His Pro Arg Ala Gln Pro Arg Thr Glu Asp Ala Ala Lys Asp Pro Asp 305 310 315 320

Pro Glu Leu Leu Lys Gln Arg Gly Arg Pro Cys Arg Phe Gly Leu Cys 325 330 335

Glu Arg Asp Pro Lys Ser His Ser Ser Ala Cys. Ala Glu Gly Tyr Thr 340 345 350

Leu Ser Arg Asp Arg Lys Tyr Cys Glu Asp Val Asn Glu Cys Ala Thr 355 360 365

Gln Asn His Gly Cys Thr Leu Gly Cys Glu Asn Thr Pro Gly Ser Tyr 370 375 380

His Cys Thr Cys Pro Thr Gly Phe Val Leu Leu Pro Asp Gly Lys Gln 385 390 395 400

Cys His Glu Leu Val Ser Cys Pro Gly Asn Val Ser Lys Cys Ser His
405 410 415

Gly	y Cys	s Vai	1 Lei 420	ı Thi	Ser	Asp	o Gly	/ Pro 425	Arç	g Cys	s Ile	Cys	9 Pro 430		a Gly
Ser	. Val	Let 435	ı Gly	/ Arc	g Asp	Gly	/ Lys		· Cys	Thr	Gly	Cys 445		: Sei	Pro
Asp	450	n Gly	/ Gly	/ Cys	Ser	Gln 455	ı Ile	: Cys	Leu	Pro	Leu 460		Pro	Gly	/ Ser
Trp 465	Glu	ı Cys	a Asp	Cys	Phe 470	Pro	Gly	Tyr	Asp	Leu 475		Ser	Asp	Arç	Lys 480
Ser	· Cys	Ala	Ala	Ser 485	Gly	Pro	Gln	Pro	Leu 490	Leu	Leu	Phe	Ala	Asn 495	Ser
Gln	Asp) Ile	500	His	Met	His	Phe	Asp 505	Gly	Thr	Asp	Tyr	Lys 510		Leu
Leu	Ser	Arg 515	Gln	Met	Gly	Met	Val 520	Phe	Ala	Leu	Asp	Tyr 525	Asp	Pro	Val
Glu	Ser 530	Lys	Ile	Tyr	Phe	Ala 535	Gln	Thr	Ala	Leu	Lys 540	Trp	Ile	Glu	Arg
545					550		Arg			555					560
				565			Leu		570					575	
			580				Val	585					590		
		595					Gln 600					605			
	610					615	Arg		;		620				
625					630		Ala			635					640
				645			Leu		650					655	
,			660				Trp	665					670	٠	
		6/5					Ser 680			·		685			
	690					695	Leu				700				
/05					/10		Ser			715					720
Gly	Gln	Asn	Arg	Val 725	Arg	Leu	Gln		Ser 730	Met	Leu	Lys		Ser 735	Ser

Leu Val Val His Pro Leu Ala Lys Pro Gly Ala Asp Pro Cys Leu Tyr Arg Asn Gly Gly Cys Glu His Ile Cys Gln Glu Ser Leu Gly Thr Ala Arg Cys Leu Cys Arg Glu Gly Phe Val Lys Ala Trp Asp Gly Lys Met Cys Leu Pro Gln Asp Tyr Pro Ile Leu Ser Gly Glu Asn Ala Asp Leu Ser Lys Glu Val Thr Ser Leu Ser Asn Ser Thr Gln Ala Glu Val Pro Asp Asp Gly Thr Glu Ser Ser Thr Leu Val Ala Glu Ile Met 825 Val Ser Gly Met Asn Tyr Glu Asp Asp Cys Gly Pro Gly Gly Cys Gly Ser His Ala Arg Cys Val Ser Asp Gly Glu Thr Ala Glu Cys Gln Cys Leu Lys Gly Phe Ala Arg Asp Gly Asn Leu Cys Ser Asp Ile Asp Glu Cys Val Leu Ala Arg Ser Asp Cys Pro Ser Thr Ser Ser Arg Cys Ile Asn Thr Glu Gly Gly Tyr Val Cys Arg Cys Ser Glu Gly Tyr Glu Gly 900 Asp Gly Ile Ser Cys Phe Asp Ile Asp Glu Cys Gln Arg Gly Ala His 920 Asn Cys Ala Glu Asn Ala Ala Cys Thr Asn Thr Glu Gly Gly Tyr Asn 935 940 Cys Thr Cys Ala Gly Arg Pro Ser Ser Pro Gly Leu Ser Cys Pro Asp Ser Thr Ala Pro Ser Leu Leu Gly Glu Asp Gly His His Leu Asp Arg 970 Asn Ser Tyr Pro Gly Cys Pro Ser Ser Tyr Asp Gly Tyr Cys Leu Asn 980 Gly Gly Val Cys Met His Ile Glu Ser Leu Asp Ser Tyr Thr Cys Asn Cys Val Ile Gly Tyr Ser Gly Asp Arg Cys Gln Thr Pro Pro Ser Ser 1015 Asp Arg Gly Pro Gln Glu Ile Glu Gly Asn Ser His Leu Pro Ser Tyr 1025 1030 Arg Pro Val Gly Pro Glu Lys Leu His Ser Leu Gln Ser Ala Asn Gly 1050 Ser Cys His Glu Arg Ala Pro Asp Leu Pro Arg Gln Thr Glu Pro Val

1060 1065 1070

Gln

<210> 141

<211> 804

<212> PRT

<213> Homo sapiens

<400> 141

Met Pro Trp Gly Arg Arg Pro Thr Trp Leu Leu Leu Ala Phe Leu Leu 1 5 10 15

Val Phe Leu Lys Ile Ser Ile Leu Ser Val Thr Ala Trp Gln Thr Gly
20 25 30

Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys
35 40 45

Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser 50 55 60

Arg Ile Asp Pro Asp Gly Thr Asn His Gln Gln Leu Val Val Asp Ala 65 70 75 80

Gly Ile Ser Ala Asp Met Asp Ile His Tyr Lys Lys Glu Arg Leu Tyr 85 90 95

Trp Val Asp Val Glu Arg Gln Val Leu Leu Arg Val Phe Leu Asn Gly
100 105 110

Thr Gly Leu Glu Lys Val Cys Asn Val Glu Arg Lys Val Ser Gly Leu 115 120 125

Ala Ile Asp Trp Ile Asp Asp Glu Val Leu Trp Val Asp Gln Gln Asn 130 135 140

Gly Val Ile Thr Val Thr Asp Met Thr Gly Lys Asn Ser Arg Val Leu 145 150 155 160

Leu Ser Ser Leu Lys His Pro Ser Asn Ile Ala Val Asp Pro Ile Glu 165 170 175

Arg Leu Met Phe Trp Ser Ser Glu Val Thr Gly Ser Leu His Arg Ala 180 185 190

His Leu Lys Gly Val Asp Val Lys Thr Leu Leu Glu Thr Gly Gly Ile 195 200 205

Ser Val Leu Thr Leu Asp Val Leu Asp Lys Arg Leu Phe Trp Val Gln 210 215 220

Asp Ser Gly Glu Gly Ser His Ala Tyr Ile His Ser Cys Asp Tyr Glu 225 230 235 240

Gly Gly Ser Val Arg Leu Ile Arg His Gln Ala Arg His Ser Leu Ser 245 250 255

Ser Met Ala Phe Phe Gly Asp Arg Ile Phe Tyr Ser Val Leu Lys Ser

260 265 270 Lys Ala Ile Trp Ile Ala Asn Lys His Thr Gly Lys Asp Thr Val Arg 280 Ile Asn Leu His Pro Ser Phe Val Thr Pro Gly Lys Leu Met Val Val 295 His Pro Arg Ala Gln Pro Arg Thr Glu Asp Ala Ala Lys Asp Pro Asp Pro Glu Leu Leu Lys Gln Arg Gly Arg Pro Cys Arg Phe Gly Leu Cys 325 Glu Arg Asp Pro Lys Ser His Ser Ser Ala Cys Ala Glu Gly Tyr Thr 340 345 Leu Ser Arg Asp Arg Lys Tyr Cys Glu Asp Val Asn Glu Cys Ala Thr Gln Asn His Gly Cys Thr Leu Gly Cys Glu Asn Thr Pro Gly Ser Tyr 375 His Cys Thr Cys Pro Thr Gly Phe Val Leu Leu Pro Asp Gly Lys Gln 395 Cys His Glu Leu Val Ser Cys Pro Gly Asn Val Ser Lys Cys Ser His 410 Gly Cys Val Leu Thr Ser Asp Gly Pro Arg Cys Ile Cys Pro Ala Gly 420 Ser Val Leu Gly Arg Asp Gly Lys Thr Cys Thr Gly Cys Ser Ser Pro Asp Asn Gly Gly Cys Ser Gln Ile Cys Leu Pro Leu Arg Pro Gly Ser . 455 Trp Glu Cys Asp Cys Phe Pro Gly Tyr Asp Leu Gln Ser Asp Arg Lys 470 ; 475 Ser Cys Ala Ala Ser Gly Pro Gln Pro Leu Leu Phe Ala Asn Ser 485 490 Gln Asp Ile Arg His Met His Phe Asp Gly Thr Asp Tyr Lys Val Leu 510 Leu Ser Arg Gln Met Gly Met Val Phe Ala Leu Asp Tyr Asp Pro Val Glu Ser Lys Ile Tyr Phe Ala Gln Thr Ala Leu Lys Trp Ile Glu Arg Ala Asn Met Asp Gly Ser Gln Arg Glu Arg Leu Ile Thr Glu Gly Val 545 550 Asp Thr Leu Glu Gly Leu Ala Leu Asp Trp Ile Gly Arg Arg Ile Tyr 565 570 Trp Thr Asp Ser Gly Lys Ser Val Val Gly Gly Ser Asp Leu Ser Gly 580 585

Lys His His Arg Ile Ile Ile Gln Glu Arg Ile Ser Arg Pro Arg Gly 595 Ile Ala Val His Pro Arg Ala Arg Arg Leu Phe Trp Thr Asp Val Gly 615 Met Ser Pro Arg Ile Glu Ser Ala Ser Leu Gln Gly Ser Asp Arg Val 630 635 Leu Ile Ala Ser Ser Asn Leu Leu Glu Pro Ser Gly Ile Thr Ile Asp. 645 650 Tyr Leu Thr Asp Thr Leu Tyr Trp Cys Asp Thr Lys Arg Ser Val Ile Glu Met Ala Asn Leu Asp Gly Ser Lys Arg Arg Leu Ile Gln Asn 680 Asp Val Gly His Pro Phe Ser Leu Ala Val Phe Glu Asp His Leu Trp 695 Val Ser Asp Trp Ala Ile Pro Ser Val Ile Arg Val Asn Lys Arg Thr 710 715 Gly Gln Asn Arg Val Arg Leu Gln Gly Ser Met Leu Lys Pro Ser Ser 725 730 Leu Val Val His Pro Leu Ala Lys Pro Gly Ala Asp Pro Cys Leu Tyr Arg Asn Gly Gly Cys Glu His Ile Cys Gln Glu Ser Leu Gly Thr

Ala Arg Cys Leu Cys Arg Glu Gly Phe Val Lys Ala Trp Asp Gly Lys

Met Cys Leu Pro Gln Asp Tyr Pro Ile Leu Ser Gly Glu Asn Ala His 795 790

Asn Cys Ala Phe

<210> 142 <211> 576 <212> PRT

<213> Homo sapiens

<400> 142

Met Pro Trp Gly Arg Pro Thr Trp Leu Leu Ala Phe Leu Leu

Val Phe Leu Lys Ile Ser Ile Leu Ser Val Thr Ala Trp Gln Thr Gly 20

Asn Cys Gln Pro Gly Pro Leu Glu Arg Ser Glu Arg Ser Gly Thr Cys

Ala Gly Pro Ala Pro Phe Leu Val Phe Ser Gln Gly Lys Ser Ile Ser 55

Arg 65	Ile	Trp	Ala	Ile	Pro 70	Ser	Val	Ile	Arg	Val 75	Asn	Lys	Arg	Thr	Gly 80
Gln	Asn	Arg	Val	Arg 85	Leu	Gln	Gly	Ser	Met 90	Leu	Lys	Pro	Ser	Ser 95	Leu
Val	Val	Val	His 100	Pro	Leu	Ala	Lys	Pro 105	Gly	Ala	Asp	Pro	Cys 110	Leu	Tyr
Arg	Asn	Gly 115	Gly	Cys	Glu	His	Ile 120	Cys	Gln	Glu	Ser	Leu 125	Gly	Thr	Ala
Arg	Cys 130	Leu	Cys	Arg	Glu	Gly 135	Phe	Val	Lys	Ala	Trp 140	Asp	Gly	Lys	Met
Cys 145	Leu	Pro	Gln	Asp	Tyr 150	Pro	Ile	Leu	Ser	Gly 155	Glu	Asn	Ala	Asp	Leu 160
Ser	Lys	Glu	Val	Thr 165	Ser	Leu	Ser	Asn	Ser 170	Thr	Gln	Ala	Glu	Val 175	Pro
Asp	Asp	Asp	Gly 180	Thr	Glu	Ser	Ser	Thr 185	Leu	Val	Ala	Glu	Ile 190	Met	Val
Ser	Gly	Met 195	Asn	Tyr	Glu	Asp	Asp 200	Cys	Gly	Pro	Gly	Gly 205	Cys	Gly	Ser
His	Ala 210	Arg	Cys	Val	Ser	Asp 215	Gly	Glu	Thr	Ala	Glu 220	Cys	Gln	Cys	Leu
Lys 225	Gly	Phe	Ala	Arg	Asp 230	Gly	Asn	Leu	Cys	Ser 235	Asp	Ile	Asp	Glu	Cys 240
Val	Leu	Ala	Arg	Ser 245	Asp	Cys	Pro	Ser	Thr 250	Ser	Ser	Arg	Cys	Ile 255	Asn
Thr	Glu	Gly	Gly 260	Tyr	Val	Cys	Arg	Cys 265	Ser	Glu	Gly	Tyr	Glu 270	Gly	Asp
Gly	Ile	Ser 275	Cys	Phe	Asp	Ile	Asp 280	Glu	Cys	Gln	Arg	Gly 285	Ala	His	Asn
Cys	Ala 290	Glu	Asn	Ala	Ala	Cys 295	Thr	Asn	Thr	Glu	Gly 300	Gly	Tyr	Asn	Cys
Thr 305	Cys	Ala	Gly	Arg	Pro 310	Ser	Ser	Pro	Gly	Leu 315	Ser	Cys	Pro	Asp	Ser 320
Thr	Ala	Pro	Ser	Leu 325	Leu	Gly	Glu	Asp	Gly 330	His	His	Leu	Asp	Arg 335	Asn
Ser	Tyr	Pro	Gly 340	Cys	Pro	Ser	Ser	Tyr 345	Asp	Gly	Tyr	Cys	Leu 350	Asn	Gly
Gly	Val	Cys 355	Met	His	Ile	Glu	Ser 360	Leu	Asp	Ser	Tyr	Thr 365	Cys	Asn	Cys
Val	Ile 370	Gly	Tyr	Ser	Gly	Asp 375	Arg	Ċys	Gln	Thr	Arg 380	Asp	Leu	Arg	Trp

Trp Glu Leu Arg His Ala Gly Tyr Gly Gln Lys His Asp Ile Met Val Val Ala Val Cys Met Val Ala Leu Val Leu Leu Leu Leu Gly Met 405 410 Trp Gly Thr Tyr Tyr Arg Thr Arg Lys Gln Leu Ser Asn Pro Pro 425 Lys Asn Pro Cys Asp Glu Pro Ser Gly Ser Val Ser Ser Ser Gly Pro 440 Asp Ser Ser Ser Gly Ala Ala Val Ala Ser Cys Pro Gln Pro Trp Phe 450 Val Val Leu Glu Lys His Gln Asp Pro Lys Asn Gly Ser Leu Pro Ala Asp Gly Thr Asn Gly Ala Val Val Asp Ala Gly Leu Ser Pro Ser Leu Gln Leu Gly Ser Val His Leu Thr Ser Trp Arg Gln Lys Pro His Ile 500 505 Asp Gly Met Gly Thr Gly Gln Ser Cys Trp Ile Pro Pro Ser Ser Asp 520 Arg Gly Pro Gln Glu Ile Glu Gly Asn Ser His Leu Pro Ser Tyr Arg 530 Pro Val Gly Pro Glu Lys Leu His Ser Leu Gln Ser Ala Asn Gly Ser 550 Cys His Glu Arg Ala Pro Asp Leu Pro Arg Gln Thr Glu Pro Val Gln 570

<210> 143 <211> 376

<212> PRT

<213> Homo sapiens

<400> 143

Met Pro Trp Gly Arg Arg Pro Thr Trp Leu Leu Leu Ala Phe Leu Leu 1 5 10 15

Val Ser Ala Glu Cys Gln Cys Leu Lys Gly Phe Ala Arg Asp Gly Asn 20 25 30

Leu Cys Ser Asp Ile Asp Glu Cys Val Leu Ala Arg Ser Asp Cys Pro 35 40 45

Ser Thr Ser Ser Arg Cys Ile Asn Thr Glu Gly Gly Tyr Val Cys Arg 50 55 60

Cys Ser Glu Gly Tyr Glu Gly Asp Gly Ile Ser Cys Phe Asp Ile Asp 65 70 75 80

Glu Cys Gln Arg Gly Ala His Asn Cys Ala Glu Asn Ala Ala Cys Thr Asn Thr Glu Gly Gly Tyr Asn Cys Thr Cys Ala Gly Arg Pro Ser Ser 105 Pro Gly Leu Ser Cys Pro Asp Ser Thr Ala Pro Ser Leu Leu Gly Glu 120 115 Asp Gly His His Leu Asp Arg Asn Ser Tyr Pro Gly Cys Pro Ser Ser 135 Tyr Asp Gly Tyr Cys Leu Asn Gly Gly Val Cys Met His Ile Glu Ser 150 Leu Asp Ser Tyr Thr Cys Asn Cys Val Ile Gly Tyr Ser Gly Asp Arg Cys Gln Thr Arg Asp Leu Arg Trp Trp Glu Leu Arg His Ala Gly Tyr Gly Gln Lys His Asp Ile Met Val Val Ala Val Cys Met Val Ala Leu 200 Val Leu Leu Leu Leu Gly Met Trp Gly Thr Tyr Tyr Arg Thr Arg Lys Gln Leu Ser Asn Pro Pro Lys Asn Pro Cys Asp Glu Pro Ser 230 235 Gly Ser Val Ser Ser Ser Gly Pro Asp Ser Ser Ser Gly Ala Ala Val Ala Ser Cys Pro Gln Pro Trp Phe Val Val Leu Glu Lys His Gln Asp Pro Lys Asn Gly Ser Leu Pro Ala Asp Gly Thr Asn Gly Ala Val Val 275 285 Asp Ala Gly Leu Ser Pro Ser Leu Gln Leu Gly Ser Val His Leu Thr Ser Trp Arg Gln Lys Pro His Ile Asp Gly Met Gly Thr Gly Gln Ser 310 Cys Trp Ile Pro Pro Ser Ser Asp Arg Gly Pro Gln Glu Ile Glu Gly 330 Asn Ser His Leu Pro Ser Tyr Arg Pro Val Gly Pro Glu Lys Leu His Ser Leu Gln Ser Ala Asn Gly Ser Cys His Glu Arg Ala Pro Asp Leu 360 Pro Arg Gln Thr Glu Pro Val Gln 375 370

<210> 144

<211> 1249

<212> PRT

<213> Homo sapiens

<400> 144

Met Gly Ala Ala Ser Gly Gln Arg Gly Arg Trp Pro Leu Ser Pro Pro l 5 10 15

Leu Leu Met Leu Ser Leu Leu Val Leu Leu Leu Gln Pro Ser Pro Ala 20 25 30

Pro Ala Leu Asp Pro Gly Leu Gln Pro Gly Asn Phe Ser Pro Asp Glu 35 40 45

Ala Gly Ala Gln Leu Phe Ala Glu Ser Tyr Asn Ser Ser Ala Glu Val 50 55 60

Val Met Phe Gln Ser Thr Val Ala Ser Trp Ala His Asp Thr Asn Ile 65 70 75 80

Thr Glu Glu Asn Ala Arg Arg Gln Glu Glu Ala Ala Leu Val Ser Gln
85 .90 95

Glu Phe Ala Glu Val Trp Gly Lys Lys Ala Lys Glu Leu Tyr Glu Ser 100 105 110

Ile Trp Gln Asn Phe Thr Asp Ser Lys Leu Arg Arg Ile Ile Gly Ser 115 120 125

Ile Arg Thr Leu Gly Pro Ala Asn Leu Pro Leu Ala Gln Arg Gln Gln 130 135 140

Tyr Asn Ser Leu Leu Ser Asn Met Ser Arg Ile Tyr Ser Thr Gly Lys 145 150 155 160

Val Cys Phe Pro Asn Lys Thr Ala Thr Cys Trp Ser Leu Asp Pro Glu 165 170 175

Leu Thr Asn Ile Leu Ala Ser Ser Arg Ser Tyr Ala Lys Leu Leu Phe 180 185 190

Ala Trp Glu Gly Trp His Asp Ala Val Gly Ile Pro Leu Lys Pro Leu 195 200 205

Tyr Gln Asp Phe Thr Ala Ile Ser Asn Glu Ala Tyr Arg Gln Asp Asp 210 215 220

Phe Ser Asp Thr Gly Ala Phe Trp Arg Ser Trp Tyr Glu Ser Pro Ser 225 230 235 240

Phe Glu Glu Ser Leu Glu His Ile Tyr His Gln Leu Glu Pro Leu Tyr 245 250 255

Leu Asn Leu His Ala Tyr Val Arg Arg Ala Leu His Arg Arg Tyr Gly 260 265 270

Asp Lys Tyr Val Asn Leu Arg Gly Pro Ile Pro Ala His Leu Leu Gly 275 280 285

Asp Met Trp Ala Gln Ser Trp Glu Asn Ile Tyr Asp Met Val Val Pro 290 295 300

Phe Pro Asp Lys Pro Asn Leu Asp Val Thr Ser Thr Met Val Gln Lys

305 310 315 320 Gly Trp Asn Ala Thr His Met Phe Arg Val Ser Glu Glu Phe Phe Thr 325 330 Ser Leu Gly Leu Ser Pro Met Pro Pro Glu Phe Trp Ala Glu Ser Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val Val Cys His Ala Ser Ala Trp Asp Phe Tyr Asn Arg Lys Asp Phe Arg Ile Lys Gln Cys Thr Arg Val Thr Met Glu Gln Leu Ala Thr Val His His Glu Met Gly His Val 395 Gln Tyr Tyr Leu Gln Tyr Lys Asp Leu His Val Ser Leu Arg Arg Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly Asp Val Leu Ala Leu Ser Val Ser Thr Pro Ala His Leu His Lys Ile Gly Leu Leu Asp His Val Thr Asn Asp Ile Glu Ser Asp Ile Asn Tyr Leu Leu Lys Met Ala Leu Glu Lys Ile Ala Phe Leu Pro Phe Gly Tyr Leu Val Asp Gln Trp Arg 470 Trp Gly Val Phe Ser Gly Arg Thr Pro Pro Ser Arg Tyr Asn Phe Asp Trp Trp Tyr Leu Arg Thr Lys Tyr Gln Gly Ile Cys Pro Pro Val Ala Arg Asn Glu Thr His Phe Asp Ala Gly Ala Lys Phe His Ile Pro Asn 520 Val Thr Pro Tyr Ile Arg Tyr Phe Val Ser Phe Val Leu Gln Phe Gln Phe His Gln Ala Leu Cys Lys Glu Ala Gly His Gln Gly Pro Leu His 555 Gln Cys Asp Ile Tyr Gln Ser Xaa Gln Ala Gly Ala Lys Leu Lys Gln 565 Val Leu Gln Ala Gly Cys Ser Arg Pro Trp Gln Glu Val Leu Lys Asp Leu Val Gly Ser Asp Ala Leu Asp Ala Lys Ala Leu Leu Glu Tyr Phe 595 600 Gln Pro Val Ser Gln Trp Leu Glu Glu Gln Asn Gln Arg Asn Gly Glu 615 Val Leu Gly Trp Pro Glu Asn Gln Trp Arg Pro Pro Leu Pro Asp Asn 630 635

Tyr	Pro	Glu	Gly	Ile 645	Asp	Leu	Glu	Thr	Asp 650	Glu	Ala	Lys	Ala	Asp 655	Arg
Phe	Val	Glu	Glu 660	Tyr	Asp	Arg	Thr	Ala 665	Gln	Val	Leu	Leu	Asn 670	Glu	Tyr
Ala	Glu	Ala 675	Asn	Trp	Gln	Tyr	Asn 680	Thr	Asn	Ile	Thr	Ile 685	Glu	Gly	Ser
Lys	Ile 690	Leu	Leu	Glu	Lys	Ser 695	Thr	Glu	Val	Ser	Asn 700	His	Thr	Leu	Lys
Tyr 705	Gly	Thr	Arg	Ala	Lys 710	Thr	Phe	Asp	Val	Ser 715	Asn	Phe	Gln	Asn	Ser 720
			Arg	725					730				-	7:35	
			Lys 740					745					750	_	
•		755	Tyr				760			_		765			
	770		Glu			775					780				
785			Leu		790					795					800
			Leu	805					810		•			815	-
			Leu 820					825					830		,
		835	Ser	•			8.40	•	i			845		_	
	850		Pro			855					860				
865			His		870					875					880
			Leu	885					890			_		895	
			Val 900					905					910		
		915	Ile				920					925			
	930		Phe			935					940				
Phe 945	Trp	Asn	Lys	Ser	Met 950	Leu	Glu	Lys	Pro	Thr 955	Asp	Gly	Arg	Glu	Val 960

Val Cys His Pro Ser Ala Trp Asp Phe Tyr Asn Gly Lys Asp Phe Arg 965 970 975

Ile Lys Gln Cys Thr Ser Val Asn Met Glu Asp Leu Val Ile Ala His 980 985 990

His Glu Met Gly His Ile Gln Tyr Phe Met Gln Tyr Lys Asp Leu Pro 995 1000 1005

Val Thr Phe Arg Glu Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly 1010 1015 1020

Asp Ile Met Ala Leu Ser Val Ser Thr Pro Lys His Leu Tyr Ser Leu 1025 1030 1035 1040

Asn Leu Leu Ser Thr Glu Gly Ser Gly Tyr Glu Tyr Asp Ile Asn Phe 1045 1050 1055

Leu Met Lys Met Ala Leu Asp Lys Ile Ala Phe Ile Pro Phe Ser Tyr 1060 1065 1070

Leu Ile Asp Gln Trp Arg Trp Arg Val Phe Asp Gly Ser Ile Thr Lys
1075 1080 1085

Glu Asn Tyr Asn Gln Glu Trp Trp Ser Leu Arg Leu Lys Tyr Gln Gly 1090 1095 1100

Leu Cys Pro Pro Val Pro Arg Ser Gln Gly Asp Phe Asp Pro Gly Ser 1105 1110 1115 1120

Lys Phe His Val Pro Ala Asn Val Pro Tyr Val Arg Tyr Phe Val Ser 1125 1130 1135

Phe Ile Ile Gln Phe Gln Phe His Glu Ala Leu Cys Arg Ala Ala Gly 1140 1145 1150

His Thr Gly Pro Leu His Lys Cys Asp Ile Tyr Gln Ser Lys Glu Ala 1155 1160 1165

Gly Lys Leu Leu Ala Asp Ala Met Lys Leu Gly Tyr Ser Lys Pro Trp 1170 1175 1180

Pro Glu Ala Met Lys Leu Ile Thr Gly Gln Pro Asn Met Ser Ala Ser 1185 1190 1195 1200

Ala Met Met Asn Tyr Phe Lys Pro Leu Thr Glu Trp Leu Val Thr Glu 1205 1210 1215

Asn Arg Arg His Gly Glu Thr Leu Gly Trp Pro Glu Tyr Asn Trp Ala 1220 1225 1230

Pro Asn Thr Gly Thr Thr Pro Thr Leu Pro Pro Ala Pro Gly Pro Ser 1235 1240 1245

Ser

<210> 145

<211> 382

<212> PRT

PCT/IL00/00766

<213> Homo sapiens

<400> 145

Met Thr Met Thr Leu His Thr Lys Ala Ser Gly Met Ala Leu Leu His 1 5 10 15

Gln Ile Gln Gly Asn Glu Leu Glu Pro Leu Asn Arg Pro Gln Leu Lys 20 25 30

Met Pro Met Glu Arg Ala Leu Gly Glu Val Tyr Val Asp Asn Ser Lys
35 40 45

Pro Thr Val Phe Asn Tyr Pro Glu Gly Ala Ala Tyr Glu Phe Asn Ala 50 55 60

Ala Ala Ala Ala Ala Ala Ala Ser Ala Pro Val Tyr Gly Gln Ser 65 70 75 80

Gly Ile Ala Tyr Gly Pro Gly Ser Glu Ala Ala Ala Phe Ser Ala Asn 85 90 95

Ser Leu Gly Ala Phe Pro Gln Leu Asn Ser Val Ser Pro Ser Pro Leu 100 105 110

Met Leu His Pro Pro Pro Gln Leu Ser Pro Phe Leu His Pro His 115 120 125

Gly Gln Gln Val Pro Tyr Tyr Leu Glu Asn Glu Pro Ser Ala Tyr Ala 130 135 140

Val Arg Asp Thr Gly Pro Pro Ala Phe Tyr Arg Ser Asn Ser Asp Asn 145 150 155 160

Arg Arg Gln Asn Gly Arg Glu Arg Leu Ser Ser Ser Asn Glu Lys Gly
165 170 175

Asn Met Ile Met Glu Ser Ala Lys Glu Thr Arg Tyr Cys Ala Val Cys 180 185 190

Asn Asp Tyr Ala Ser Gly Tyr His Tyr Gly Val Trp Ser Cys Glu Gly
195 200 205

Cys Lys Ala Phe Phe Lys Arg Ser Ile Gln Gly His Asn Asp Tyr Met 210 215 220

Cys Pro Ala Thr Asn Gln Cys Thr Ile Asp Lys Asn Arg Arg Lys Ser 235 230 235

Cys Gln Ala Cys Arg Leu Arg Lys Cys Tyr Glu Val Gly Met Met Lys
245 250 255

Gly Gly Ile Arg Lys Asp Arg Arg Gly Gly Arg Met Leu Lys His Lys 260 265 270

Arg Gln Arg Asp Asp Leu Glu Gly Arg Asn Glu Met Gly Ala Ser Gly 275 280 285

Asp Met Arg Ala Ala Asn Leu Trp Pro Ser Pro Leu Val Ile Lys His 290 295 300

Thr Lys Lys Asn Ser Pro Ala Leu Ser Leu Thr Ala Asp Gln Met Val

305 310 315 320 Ser Ala Leu Leu Asp Ala Glu Pro Pro Met Ile Tyr Ser Glu Tyr Asp 330 Pro Ser Arg Pro Phe Ser Glu Ala Ser Met Met Gly Leu Leu Thr Asn Leu Ala Asp Arg Glu Leu Val His Met Ile Asn Trp Ala Lys Arg Val Pro Gly Lys Asp Ala Lys Leu Asn Phe Tyr Val Lys Ser Glu 375 <210> 146 <211> 345 <212> PRT <213> Homo sapiens <400> 146 Met Val Pro Gln Ala His Gly Leu Leu Leu Cys Phe Leu Leu Gln Leu Gln Gly Pro Leu Gly Thr Ala Val Phe Ile Thr Gln Glu Glu Ala His Gly Val Leu His Arg Gln Arg Arg Ala Asn Ser Leu Leu Glu Glu 40 Leu Trp Pro Gly Ser Leu Glu Arg Glu Cys Asn Glu Glu Gln Cys Ser 55 Phe Glu Glu Ala Arg Glu Ile Phe Lys Ser Pro Glu Arg Thr Lys Gln Phe Trp Ile Val Tyr Ser Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys Gln Asn Gly Gly Thr Cys Gln Asp His Leu Lys Ser Tyr Val Cys Phe 105 Cys Leu Leu Asp Phe Glu Gly Ala Val Leu Leu Asp Ala Arg Trp Ile 120 Val Thr Ala Ala His Cys Phe Asp Asn Ile Arg Tyr Trp Gly Asn Ile Thr Val Val Met Gly Glu His Asp Phe Ser Glu Lys Asp Gly Asp Glu 145 150 Gln Val Arg Arg Val Thr Gln Val Ile Met Pro Asp Lys Tyr Ile Arg 165 Gly Lys Ile Asn His Asp Ile Ala Leu Leu Arg Leu His Arg Pro Val 180 185 Thr Phe Thr Asp Tyr Val Val Pro Leu Cys Leu Pro Glu Lys Ser Phe

Ser Glu Asn Thr Leu Ala Arg Ile Arg Phe Ser Arg Val Ser Gly Trp

210 215 220

Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Ser Ile 225 230 235 240

Glu Val Pro Arg Leu Met Thr Gln Asp Cys Leu Glu His Ala Lys His
245 250 255

Ser Ser Asn Thr Pro Lys Ile Thr Glu Asn Met Phe Cys Ala Gly Tyr 260 265 270

Met Asp Gly Thr Lys Asp Ala Cys Lys Gly Asp Ser Gly Gly Pro His 275 280 285

Ala Thr His Tyr His Gly Thr Trp Tyr Leu Thr Gly Val Val Ser Trp 290 295 300

Gly Glu Gly Cys Ala Ala Ile Gly His Ile Gly Val Tyr Thr Arg Val 305 310 315 320

Ser Gln Tyr Ile Asp Trp Leu Val Arg His Met Asp Ser Lys Leu Gln 325 330 335

Val Gly Val Phe Arg Leu Pro Leu Leu 340 345

<210> 147

<211> 103

<212> PRT

<213> Homo sapiens

<400> 147

Met Gly Phe Leu Lys Phe Ser Pro Phe Leu Val Val Ser Ile Leu Leu 1 5 15

Leu Ala Leu Val Gln Asp Tyr Met Gln Met Lys Ala Arg Glu Leu Glu 20 25 30

Gln Glu Glu Gln Glu Ala Glu Gly Ser Ser Leu Asp Ser Pro Arg
35. 40 45

Ser Lys Arg Cys Gly Asn Leu Ser Thr Cys Met Leu Gly Thr Tyr Thr 50 55 60

Gln Asp Leu Asn Lys Phe His Thr Phe Pro Gln Thr Ser Ile Gly Val 65 70 75 80

Glu Ala Pro Gly Lys Lys Arg Asp Val Ala Lys Asp Leu Glu Thr Asn 85 90 95

His Gln Ser His Phe Gly Asn 100

<210> 148

<211> 525

<212> PRT

<213> Homo sapiens

<400> 148

PCT/IL00/00766

Met	Ala	Thr	Leu	Leu	Arg	Ser	Lvs	Leu	Thr	Asn	Val	Ala	Thr	S0=	1/2)
1					-		-1-				, , ,	1114	1111	Ser	vai
				2					10					15	
														~~	

- Ser Asn Lys Ser Gln Ala Lys Val Ser Gly Met Phe Ala Arg Met Gly 20 25 30
- Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His Cys Asp 35 40 45
- Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile Leu Lys 50 55 60
- Ser Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro Val Glu 65 70 75 80
- Gly Asp Ile His Tyr Gln Arg Gly Gly Ala Pro Leu Pro Pro Ser Gly 85 90 95
- Ser Lys Asp Gln Ala Val Gly Ala Gly Gly Glu Phe Gly Gly His Asp 100 105 110
- Lys Pro Lys Ile Thr Ala Trp Glu Ala Gly Trp Asn Val Thr Asn Ala 115 120 125
- Ile Gln Gly Met Phe Val Leu Gly Leu Pro Tyr Ala Ile Leu His Gly 130 135 140
- Gly Tyr Leu Gly Leu Phe Leu Ile Ile Phe Ala Ala Val Val Cys Cys 145 150 155 160
- Tyr Thr Gly Lys Ile Leu Ile Ala Cys Leu Tyr Glu Glu Asn Glu Asp 165 170 175
- Gly Glu Val Val Arg Val Arg Asp Ser Tyr Val Ala Ile Ala Asn Ala 180 185 190
- Cys Cys Ala Pro Arg Phe Pro Thr Leu Gly Gly Arg Val Val Asn Val 195 200 205
- Ala Gln Ile Ile Glu Leu Val Met Thr Cys Ile Leu Tyr Val Val Val 210 215 220
- Ser Gly Asn Leu Met Tyr Asn Ser Phe Pro Gly Leu Pro Val Ser Gln 235 240
- Lys Ser Trp Ser Ile Ile Ala Thr Ala Val Leu Leu Pro Cys Ala Phe 245 250 255
- Leu Lys Asn Leu Lys Ala Val Ser Lys Phe Ser Leu Leu Cys Thr Leu 260 265 270
- Ala His Phe Val Ile Asn Ile Leu Val Ile Ala Tyr Cys Leu Ser Arg 275 280 285
- Ala Arg Asp Trp Ala Trp Glu Lys Val Lys Phe Tyr Ile Asp Val Lys 290 295 300
- Lys Phe Pro Ile Ser Ile Gly Ile Ile Val Phe Ser Tyr Thr Ser Gln 305 310 315 320
- Ile Phe Leu Pro Ser Leu Glu Gly Asn Met Gln Gln Pro Ser Glu Phe

325 330 335

His Cys Met Met Asn Trp Thr His Ile Ala Ala Cys Val Leu Lys Gly 340 345 350

Leu Phe Ala Leu Val Ala Tyr Leu Thr Trp Ala Asp Glu Thr Lys Glu 355 360 365

Val Ile Thr Asp Asn Leu Pro Gly Ser Ile Arg Ala Val Val Asn Leu 370 380

Phe Leu Val Ala Lys Ala Leu Leu Ser Tyr Pro Leu Pro Phe Phe Ala 385 390 395 400

Ala Val Glu Val Leu Glu Lys Ser Leu Phe Gln Glu Gly Ser Arg Ala
405 410 415

Phe Phe Pro Ala Cys Tyr Gly Gly Asp Gly Arg Leu Lys Ser Trp Glu 420 425 430

Leu Thr Leu Arg Cys Ala Leu Val Val Phe Thr Leu Leu Met Ala Ile 435 440 445

Tyr Val Pro His Phe Ala Leu Leu Met Gly Leu Thr Gly Ser Leu Thr 450 455 460

Gly Ala Gly Leu Cys Phe Leu Leu Pro Ser Leu Phe His Leu Arg Leu 465 470 475 480

Leu Trp Arg Lys Leu Leu Trp His Gln Val Phe Phe Asp Val Ala Ile
485 490 495

Phe Val Ile Gly Gly Ile Cys Ser Val Ser Gly Phe Val His Ser Leu 500 505 510

Glu Gly Leu Ile Glu Ala Tyr Arg Thr Asn Ala Glu Asp 515 520 525

<210> 149

<211> 400

<212> PRT

<213> Homo sapiens

<400> 149

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu 1 5 10 15

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly 50 55 60

Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn 65 70 75 80

Lys Thr Gly Thr Gln Tyr Leu Leu Arg Val Ala Asn Arg Leu Phe Gly

90 . 95 85 Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys 105 Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu 125 120 Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly 135 Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg 150 Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln 170 Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Asn 180 185 Glu Glu Lys Pro Val Gln Met Met Phe Lys Gln Ser Thr Phe Lys Lys Thr Tyr Ile Gly Glu Ile Phe Thr Gln Ile Leu Val Leu Pro Tyr Val 215 Gly Lys Glu Leu Asn Met Ile Ile Met Leu Pro Asp Glu Thr Thr Asp 230 Leu Arg Thr Val Glu Lys Glu Leu Thr Tyr Glu Lys Phe Val Glu Trp Thr Arg Leu Asp Met Met Asp Glu Glu Glu Val Glu Val Ser Leu Pro Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn 280 Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Wis Lys Ser Phe 310 Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala 325 330

Ile Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp 340

His Pro Phe Leu Phe Phe Ile Gln His Ser Lys Thr Asn Gly Ile Leu 360

Phe Cys Gly Arg Gln Leu Met Asn Phe Ser Pro Asp Ser Ser Ala Gly 375

Cys Cys Asn Val Xaa Leu Phe Pro Ser Pro Trp Gly Gly Gly Gly 390

<210> 150 <211> 372 <212> PRT <213> Homo sapiens

<400> 150

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu 1 5 10 15

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met 20 25 30

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn 35 40 45

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly 50 55 60

Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn
65 70 75 80

Lys Thr Gly Thr Gln Tyr Leu Leu Arg Val Ala Asn Arg Leu Phe Gly
85 90 95

Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys
100 105 110

Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu 115 120 125

Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly
130 135 140

Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg
145 150 155 160

Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln
165 170 175

Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Asn 180 185 190

Glu Glu Lys Pro Val Gln Met Met Phe Lys Gln Ser Thr Phe Lys Lys 195 200 205

Thr Tyr Ile Gly Glu Ile Phe Thr Gln Ile Leu Val Leu Pro Tyr Val 210 215 220

Gly Lys Glu Leu Asn Met Ile Ile Met Leu Pro Asp Glu Thr Thr Asp 225 230 235 240

Leu Arg Thr Val Glu Lys Glu Leu Thr Tyr Glu Lys Phe Val Glu Trp
245 250 255

Thr Arg Leu Asp Met Met Asp Glu Glu Glu Val Glu Val Ser Leu Pro 260 265 270

Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn 275 280 285

Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly 295 Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Val His Lys Ser Phe 310 Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala 330 Ile Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp 340 345 His Pro Phe Leu Phe Phe Ile Gln Gln Arg Ile Pro Leu Val Leu Leu 360

Cys Trp Ser Thr 370

<210> 151 <211> 560 <212> PRT <213> Homo sapiens

<400> 151 Met Phe Pro Asp Leu Val Gln Leu Ile Cys Ala Tyr Cys His Thr Arg

Asp Ile Leu Leu Pro Leu Gln Leu Pro Arg Ala Ile His His Ala

Ala Thr His Lys Glu Leu Glu Ala Ile Ser His Leu Gly Ile Glu Phe 40

Trp Ser Ser Ser Leu Asn Ile Lys Ala Gln Arg Gly Pro Ala Gly Gly

Pro Val Leu Pro Gln Leu Lys Ala Arg Ser Pro Gln Glu Leu Asp Gln

Gly Thr Gly Ala Ala Leu Cys Phe Phe Asn Pro Leu Phe Pro Gly Asp

Leu Gly Pro Thr Lys Arg Glu Lys Phe Lys Arg Ser Phe Lys Val Arg 100

Val Ser Thr Glu Thr Ser Ser Pro Leu Ser Pro Pro Ala Val Pro Pro 120

Pro Pro Val Pro Val Leu Pro Gly Ala Val Pro Ser Gln Thr Glu Arg 135

Leu Pro Pro Cys Gln Leu Leu Arg Arg Glu Ser Ser Val Gly Tyr Arg 150 155

Val Pro Ala Gly Ser Gly Pro Ser Leu Pro Pro Met Pro Ser Leu Gln 165 170

Glu Val Asp Cys Gly Ser Pro Ser Ser Ser Glu Glu Glu Gly Val Pro 180 185 190

Gly	Ser	Arg 195	Gly	Ser	Pro	Ala	Thr 200	Ser	Pro	His	Leu	Gly 205	Arg	Arg	Arg
Pro	Leu 210	Leu	Arg	Ser	Met	Ser 215	Ala	Ala	Phe	Cys	Ser 220	Leu	Leu	Ala	Pro
Glu 225	Arg	Gln	Val	Gly	Arg 230	Ala	Ala	Ala	Ala	Leu 235	Met	Gln	Asp	Arg	His 240
Thr	Ala	Ala	Gly	Gln 245	Leu	Val	Gln	Asp	Leu 250	Leu	Thr	Gln	Val	Arg 255	Asp
Gly	Gln	Arg	Pro 260	Gln	Glu	Leu	Glu	Gly 265	Ile	Arg	Gln	Ala	Leu 270	Ser	Arg
Ala	Arg	Ala 275	Met	Leu	Ser	Ala	Glu 280	Leu	Gly	Pro	Glu	Lys 285	Leu	Val	Ser
Pro	Lys 290	Arg	Leu	Glu	His	Val 295	Leu	Glu	Lys	Ser	Leu 300	His	Cys	Ser	Val
Leu 305	Lys	Pro	Leu	Arg	Pro 310	Ile	Leu	Ala	Ala	Arg 315	Leu	Arg	Arg	Arg	Leu 320
Ala	Ala	Asp	Gly	Ser 325	Leu	Gly	Arg	Leu	Ala 330	Glu	Gly	Leu	Arg	Leu 335	Ala
			Gly 340					345					350		
Pro	Val	Glu 355	Leu	Glu	Gln	Val	Arg 360	Gln	Lys	Leu	Leu	Gln 365	Leu	Val	Arg
	370		Pro			375		-			380				-
385		_	Met		390				ı	395					400
Asp	Gly	Phe	Leu	Pro 405	Leu	Leu	Ser	Leu	Val 410	Leu	Ala	His	Cys	Asp 415	Leu
			Leu 420					425					430		
Ser	Leu	Leu 435	Thr	Gly	Glu	Gly	Gly 440	Tyr	Tyr	Leu	Thr	Ser 445	Leu	Ser	Ala
Ser	Leu 450	Ala	Leu	Leu	Ser	Gly 455	Leu	Gly	Gln	Ala	His 460	Thr	Leu	Pro	Leu
Ser 465	Pro	Val	Gln	Glu	Leu 470	Arg	Arg	Ser	Leu	Ser 475	Leu	Trp	Glu	Gln	Arg 480
Arg	Leu	Pro	Ala	Thr 485	His	Cys	Phe	Gln	Val 490	Thr	Gly	Pro	Pro	Pro 495	Cys
Pro	Gln	Ser	Gln 500	Thr	Pro	Ser	Pro	Pro 505	Xaa	Thr	Phe	Leu	Ser 510	Leu	Val

PCT/IL00/00766

Lys Ser Pro Asp Ser Val Asp Arg Ser Trp Val Leu Ile Leu Ala Leu 515 520 525

His Trp Val Val Gly Thr Trp Ala Ser Tyr Leu Thr Thr Ser Cys Leu 530 535 540

Ser Phe Leu Ile Ser Lys Met Gly Val Ile Gly Pro Thr Ser Trp Gly 545 550 555 560

<210> 152

<211> 437

<212> PRT

<213> Homo sapiens

<400> 152

Met Leu Ile Ala Ala Gly Pro Ala Arg Thr Gly Val Gly Pro Ala Arg
1 5 10 15

Ile Lys Gly Ala Gln Ala Gly Trp Ala Phe His Arg Pro Ser Ala Leu 20 25 30

Cys Ser Arg Gly Ala Gly Gln Ala Xaa Ala Ser Glu Leu Ala Ser Arg 35 40 45

His Arg Gly Gly Ala Ala Ala Val Arg Thr Arg Gln Ala Asn Pro Thr 50 55 60

Gln Lys Ser Pro Pro Pro Asp Ser Gln Val Ala Ala Ala Ser Leu Ala 65 70 75 80

His Ala Glu Ser Gly Gly Ala Gly Ser Pro Leu Arg Pro Ala Ser Ala 85 90 95

Leu Ser Ser Ser Pro Phe Pro Phe Phe Ser Leu Ser Ser Pro Leu Ser 100 105 110

Leu Pro Ala Phe Ala Gln Pro Arg Ala Met Ser Asp Ala Ser Leu Arg 115 120 125

Ser Thr Ser Thr Met Glu Arg Leu Val Ala Arg Gly Thr Phe Pro Val 130 135 140

Leu Val Arg Thr Ser Ala Cys Arg Ser Leu Phe Gly Pro Val Asp His 145 150 155 160

Glu Glu Leu Ser Arg Glu Leu Gln Ala Arg Leu Ala Glu Leu Asn Ala 165 170 175

Glu Asp Gln Asn Arg Trp Asp Tyr Asp Phe Gln Gln Asp Met Pro Leu 180 185 190

Arg Gly Pro Gly Arg Leu Gln Trp Thr Glu Val Asp Ser Asp Ser Val 195 200 205

Pro Ala Phe Tyr Arg Glu Thr Val Gln Val Gly Arg Cys Arg Leu Leu 210 215 220 PCT/IL00/00766

Leu Ala Pro Arg Pro Val Ala Val Ala Val Ala Val Ser Pro Pro Leu 230 235 Glu Pro Ala Ala Glu Ser Leu Asp Gly Leu Glu Glu Ala Pro Glu Gln 245 250 Leu Pro Ser Val Pro Val Pro Ala Pro Ala Ser Thr Pro Pro Pro Val 260 265 Pro Val Leu Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Val Ala Ala 280 Pro Val Ala Ala Pro Val Ala Val Pro Val Leu Ala Pro Ala Pro Ala 295 Pro Ala Pro Ala Pro Ala Pro Ala Pro Val Ala Ala Pro Ala 310 Pro Ala 325 330 Pro Asp Ala Ala Pro Gln Glu Ser Ala Glu Gln Gly Ala Asn Gln Gly Gln Arg Gly Gln Glu Pro Leu Ala Asp Gln Leu His Ser Gly Ile Ser Gly Arg Pro Ala Ala Gly Thr Ala Ala Ala Ser Ala Asn Gly Ala Ala 375 Ile Lys Lys Leu Ser Gly Pro Leu Ile Ser Asp Phe Phe Ala Lys Arg 395 Lys Arg Ser Ala Pro Glu Lys Ser Ser Gly Asp Val Pro Ala Pro Cys Pro Ser Pro Ser Ala Ala Pro Gly Val Gly Ser Val Glu Gln Thr Pro 425 420 Arg Lys Arg Leu Arg 435 <210> 153 <211> 172 <212> PRT <213> Homo sapiens

<400> 153

Met Glu Pro Ala Ala Gly Ser Ser Met Glu Pro Ser Ala Asp Trp Leu
1 5 10 15

Ala Ser Ala Ala Arg Gly Leu Val Glu Lys Val Arg Gln Leu Leu 20 25 30

Glu Ala Gly Ala Asp Pro Asn Ala Pro Asn Ser Tyr Gly Arg Arg Pro
35 40 45

Ile Gln Val Met Met Met Gly Ser Ala Arg Val Ala Glu Leu Leu 50 55 60

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Leu His Gly Ala Glu Pro Asn Cys Ala Asp Pro Ala Thr Leu Thr Arg
65 70 75 80
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Pro Val His Asp Ala Ala Arg Glu Gly Phe Leu Asp Thr Leu Val Val 85 90 95

Leu His Arg Ala Gly Ala Arg Leu Asp Val Arg Asp Ala Trp Gly Arg 100 105 110

Leu Pro Val Asp Leu Ala Glu Glu Leu Gly His Arg Asp Val Ala Arg 115 120 125

Tyr Leu Arg Ala Ala Ala Gly Gly Thr Arg Gly Ser Asn His Ala Arg 130 135 140

Ile Asp Ala Ala Glu Gly Pro Ser Val Thr Ala Ser Ile Gln Val Pro 145 150 155 160

Gly Gly Glu Glu Gly Asp Phe Gly Ser Ser Tyr Ser 165 170

<210> 154

<211> 174

<212> PRT

<213> Homo sapiens

<400> 154

Met Arg Glu Glu Asn Lys Gly Met Pro Ser Gly Gly Gly Ser Asp Glu
1 5 10 15

Gly Leu Ala Ser Ala Ala Ala Arg Gly Leu Val Glu Lys Val Arg Gln 20 25 30

Leu Leu Glu Ala Gly Ala Asp Pro Asn Gly Val Asn Arg Phe Gly Arg 35 40 45

Arg Ala Ile Gln Val Met Met Gly Ser Ala Arg Val Ala Glu Leu 50 60

Leu Leu Leu His Gly Ala Glu Pro Asn Cys Ala Asp Pro Ala Thr Leu 65 70 75 80

Thr Arg Pro Val His Asp Ala Ala Arg Glu Gly Phe Leu Asp Thr Leu 85 90 95

Val Val Leu His Arg Ala Gly Ala Arg Leu Asp Val Arg Asp Ala Trp 100 105 110

Gly Arg Leu Pro Val Asp Leu Ala Glu Glu Leu Gly His Arg Asp Val 115 120 125

Ala Arg Tyr Leu Arg Ala Ala Gly Gly Thr Arg Gly Ser Asn His
130 135 140

Ala Arg Ile Asp Ala Ala Glu Gly Pro Ser Val Thr Ala Ser Ile Gln 145 150 155 160

Val Pro Gly Gly Glu Glu Gly Asp Phe Gly Ser Ser Tyr Ser 165 170

- <210> 155 <211> 349 <212> PRT <213> Homo sapiens <400> 155 Met Lys His Ser Leu Asn Ala Leu Leu Ile Phe Leu Ile Ile Thr Ser Ala Trp Gly Gly Ser Lys Gly Pro Leu Asp Gln Leu Glu Lys Gly Gly
- Glu Thr Ala Gln Ser Ala Asp Pro Gln Trp Glu Gln Leu Asn Asn Lys Asn Leu Ser Met Pro Leu Leu Pro Ala Asp Phe His Lys Glu Asn Thr Val Thr Asn Asp Trp Ile Pro Glu Gly Glu Glu Asp Asp Tyr Leu
- Asp Leu Glu Lys Ile Phe Ser Glu Asp Asp Asp Tyr Ile Asp Ile Val
- Asp Ser Leu Ser Val Ser Pro Thr Asp Ser Asp Val Ser Ala Gly Asn
- Ile Leu Gln Leu Phe His Gly Lys Ser Arg Ile Gln Arg Leu Asn Ile 120
- Leu Asn Ala Lys Phe Ala Phe Asn Leu Tyr Arg Val Leu Lys Asp Gln
- Val Asn Thr Phe Asp Asn Ile Phe Ile Ala Pro Val Gly Ile Ser Thr 150
- Ala Met Gly Met Ile Ser Leu Gly Leu Lys Gly Glu Thr His Glu Gln 170
- Val His Ser Ile Leu His Phe Lys Asp Phe Val Asn Ala Ser Ser Lys
- Tyr Glu Ile Thr Thr Ile His Asn Leu Phe Arg Lys Leu Thr His Arg 200
- Leu Phe Arg Arg Asn Phe Gly Tyr Thr Leu Arg Ser Val Asn Asp Leu 210 220
- Tyr Ile Gln Lys Gln Phe Pro Ile Leu Leu Asp Phe Lys Thr Lys Val
- Arg Glu Tyr Tyr Phe Ala Glu Ala Gln Ile Ala Asp Phe Ser Asp Pro 245 250
- Ala Phe Ile Ser Lys Thr Asn Asn His Ile Met Lys Leu Thr Lys Gly 265
- Leu Ile Lys Asp Ala Leu Glu Asn Ile Asp Pro Ala Thr Gln Met Met 280

Ile Leu Asn Cys Ile Tyr Phe Lys Gly Ser Trp Val Asn Lys Phe Pro 290 295 300

Val Glu Met Thr His Asn His Asn Phe Arg Leu Asn Glu Arg Glu Val 305 310 315 320

Val Lys Val Ser Met Met Gln Thr Lys Gly Asn Phe Leu Ala Ser Cys 325 330 335

<210> 156

<211> 211

<212> PRT

<213> Homo sapiens

<400> 156

Met Asp Pro Ala Arg Pro Leu Gly Leu Ser Ile Leu Leu Leu Phe Leu 1 5 15

Thr Glu Ala Ala Leu Gly Asp Ala Ala Gln Glu Pro Thr Gly Asn Asn 20 25 30

Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu 35 40 45

Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe 50 60

Leu Tyr Gly Gly Cys Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu 65 70 75 80

Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys 85 90 95

Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys 100 105 110

Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly 115 120 125

Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr 130 135 140

Cys Met Gly Phe Cys Ala Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser 145 150 155 160

Pro Lys Asp Glu Gly Leu Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe 165 170 175

Asn Pro Arg Tyr Arg Thr Cys Asp Ala Phe Thr Tyr Thr Gly Cys Gly
180 185 190

Gly Asn Asp Asn Asn Phe Val Thr Val Gln Lys Met Arg Asp Cys Ala 195 200 205

Leu Pro Met 210

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<210> 157
<211> 210
<212> PRT
<213> Homo sapiens
<400> 157
Met Asp Pro Ala Arg Pro Leu Gly Leu Ser Ile Leu Leu Leu Phe Leu
Thr Glu Ala Ala Leu Gly Asp Ala Ala Gln Glu Pro Thr Gly Asn Asn
Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu
Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe
Leu Tyr Gly Gly Cys Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu
Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys
Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys
Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly
        115
                            120
Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr
                        135
Cys Met Gly Phe Cys Ala Pro Lys Lys Lys Tyr Arg Thr Cys Asp Ala
Phe Thr Tyr Thr Gly Cys Gly Gly Asn Asp Asn Asn Phe Val Ser Arg
                165
                                     170
Glu Asp Cys Lys Arg Ala Cys Ala Lys Ala Leu Lys Lys Lys Lys
                                185
Met Pro Lys Leu Arg Phe Ala Ser Arg Ile Arg Lys Ile Arg Lys Lys
Gln Phe
    210
<210> 158
<211> 225
<212> PRT
<213> Homo sapiens
<400> 158
Met Ile Tyr Thr Met Lys Lys Val His Ala Leu Trp Ala Ser Val Cys
Leu Leu Leu Asn Leu Ala Pro Ala Pro Leu Asn Ala Asp Ser Glu Glu
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25

20

Asp Glu Glu His Thr Ile Ile Thr Asp Thr Glu Leu Pro Pro Leu Lys Leu Met His Ser Phe Cys Ala Phe Lys Ala Asp Asp Gly Pro Cys Lys Ala Ile Met Lys Arg Phe Phe Phe Asn Ile Phe Thr Arg Gln Cys Glu Glu Phe Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn Arg Phe Glu Ser 90 Leu Glu Glu Cys Lys Lys Met Cys Thr Arg Asp Asn Ala Asn Arg Ile 105 Ile Lys Thr Thr Leu Gln Gln Glu Lys Pro Asp Phe Cys Phe Leu Glu 120 Glu Asp Pro Gly Ile Cys Arg Gly Tyr Ile Thr Arg Tyr Phe Tyr Asn 130 Asn Gln Thr Lys Gln Cys Glu Arg Phe Lys Tyr Gly Gly Cys Leu Gly Asn Met Asn Asn Phe Glu Thr Leu Glu Glu Cys Lys Asn Ile Cys Glu 170 Asp Gly Pro Asn Gly Phe Gln Val Asp Asn Tyr Gly Thr Gln Leu Asn 180 Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser Leu Phe Gly Lys Asn Leu Val Asp Phe Ile Ala Ser Arg Lys Leu Leu Ser 215 Cys 225 <210> 159 <211> 636 <212> PRT <213> Homo sapiens Met Ala Ser Arg Leu Thr Leu Leu Thr Leu Leu Leu Leu Leu Leu Ala Gly Asp Arg Ala Ser Ser Asn Pro Asn Ala Thr Ser Ser Ser Gln Asp Pro Glu Ser Leu Gln Asp Arg Gly Glu Gly Lys Val Ala Thr Thr 40 Val Ile Ser Lys Met Leu Phe Val Glu Pro Ile Leu Glu Val Ser Ser

Leu Pro Thr Thr Asn Ser Thr Thr Asn Ser Ala Thr Lys Ile Thr Ala

70

Asn Thr Thr Asp Glu Pro Thr Thr Gln Pro Thr Thr Glu Pro Thr Thr Gln Pro Thr Ile Gln Pro Thr Gln Pro Thr Thr Gln Leu Pro Thr Asp 105 Ser Pro Thr Gln Pro Thr Thr Gly Ser Phe Cys Pro Gly Pro Val Thr Leu Cys Ser Asp Leu Glu Ser His Ser Thr Glu Ala Val Leu Gly Asp Ala Leu Val Asp Phe Ser Leu Lys Leu Tyr His Ala Phe Ser Ala Met 150 155 Lys Lys Val Glu Thr Asn Met Ala Phe Ser Pro Phe Ser Ile Ala Ser 165 170 Leu Leu Thr Gln Val Leu Leu Gly Ala Gly Glu Asn Thr Lys Thr Asn Leu Glu Ser Ile Leu Ser Tyr Pro Lys Asp Phe Thr Cys Val His Gln 200 Ala Leu Lys Gly Phe Thr Thr Lys Gly Val Thr Ser Val Ser Gln Ile Phe His Ser Pro Val Asp Trp Arg Leu Gln Ser Lys Ser Gln Glu 225 230 235 Val Leu Ser Gln Thr Ser Thr Lys Ala Arg Lys Gln Ser Leu Phe Arg Ala Lys Ile Lys Gly Arg Lys Glu Gly Lys Ser Arg Gln Met Glu Phe Asn Ile Ser Lys Arg Leu Ser Cys Arg Ala Ile Val His Ser Lys Leu 275 280 Arg Gln Arg Arg Leu Gly Ala Thr Ser Leu Val Leu Gly Ser Gly Phe Thr Phe Phe Gly Pro Tyr Leu Pro His Leu Glu Glu Glu Trp Ala Gly 305 310 315 Pro Arg Ser Thr Met Pro Tyr Ser Leu Ser Glu Gln Ile Glu Pro Lys Lys Ala Cys Ser Leu Ser Asn Cys Ala His Gly Lys Asn Asp Val Phe 345 Arg Thr Tyr Cys Phe Pro Phe Leu Lys Tyr Pro Pro Asp Leu Ala Ile 355 360 Arg Asp Thr Phe Val Asn Ala Ser Arg Thr Leu Tyr Ser Ser Ser Pro 375 Arg Val Leu Ser Asn Asn Ser Asp Ala Asn Leu Glu Leu Ile Asn Thr 395

Trp Val Ala Lys Asn Thr Asn Asn Lys Ile Ser Arg Leu Leu Asp Ser 405 Leu Pro Ser Asp Thr Arg Leu Val Leu Leu Asn Ala Ile Tyr Leu Ser 425 Ala Lys Trp Lys Thr Thr Phe Asp Pro Lys Lys Thr Arg Met Glu Pro 440 Phe His Phe Lys Asn Ser Val Ile Lys Val Pro Met Met Asn Ser Lys Lys Tyr Pro Val Ala His Phe Ile Asp Gln Thr Leu Lys Ala Lys Val 470 Gly Gln Leu Gln Leu Ser His Asn Leu Ser Leu Val Ile Leu Val Pro 490 Gln Asn Leu Lys His Arg Leu Glu Asp Met Glu Gln Ala Leu Ser Pro 505 500 Ser Val Phe Lys Ala Ile Met Glu Lys Leu Glu Met Ser Lys Phe Gln 520 Pro Thr Leu Leu Thr Leu Pro Arg Ile Lys Val Thr Thr Ser Gln Asp Met Leu Ser Ile Met Glu Lys Leu Glu Phe Phe Asp Phe Ser Tyr Asp 550 **555**: Leu Asn Leu Cys Gly Leu Thr Glu Asp Pro Asp Leu Gln Val Ser Ala 570 Met Gln His Gln Thr Val Leu Glu Leu Thr Glu Thr Gly Val Glu Ala Ala Ala Ala Ser Ala Ile Ser Val Ala Arg Thr Leu Leu Val Phe Glu 600 605 Val Gln Gln Pro Phe Leu Phe Val Leu Trp Asp Gln Gln His Lys Phe 615 610 Pro Val Phe Met Gly Arg Val Tyr Asp Pro Arg Ala 630 <210> 160 <211> 389 <212> PRT <213> Homo sapiens <400> 160 Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn 35 40 45 PCT/IL00/00766

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly 50 55 60

- Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn 65 70 75 80
- Lys Thr Gly Thr Gln Tyr Leu Leu Arg Met Ala Asn Arg Leu Phe Gly 85 90 95
- Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys
- Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu 115 120 125
- Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly 130 135 140
- Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg 145 150 155 160
- Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln 165 170 175
- Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Asn 180 185 190
- Glu Glu Lys Pro Val Gln Met Met Phe Lys Gln Ser Thr Phe Lys Lys 195 200 205
- Thr Tyr Ile Gly Glu Ile Phe Thr Gln Ile Leu Val Leu Pro Tyr Val 210 215 220
- Gly Lys Glu Leu Asn Met Ile Ile Met Leu Pro Asp Glu Thr Thr Asp 225 230 235 240
- Leu Arg Thr Val Glu Lys Glu Leu Thr Tyr Glu Lys Phe Val Glu Trp 245 250 255
- Thr Arg Leu Asp Met Met Asp Glu Glu Val Glu Val Ser Leu Pro 260 265 270
- Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn 275 280 285
- Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly 290 295 300
- Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Val His Lys Ser Phe 305 310 315 320
- Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala 325 330 335
- Ile Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp 340 345 350
- His Pro Phe Leu Phe Phe Ile Gln His Ser Cys Pro Leu Thr Leu His 355
- Ser Val Pro Ala Thr Gln Val Ala Leu Ser Val Gln Trp Trp Gln Phe

370 375 380

Arg Asn Lys Gly Pro 385

<210> 161

<211> 204

<212> PRT

<213> Homo sapiens

<400> 161

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu 1 5 10 15

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met 20 25 30

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn 35 40 45

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly 50 55 60

Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn 65 70 75 80

Lys Thr Gly Thr Gln Tyr Leu Leu Arg Met Ala Asn Arg Leu Phe Gly
85 90 95

Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys
100 105 110

Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu 115 120 125

Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly
130 135 140

Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg 145 150 155 160

Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln
165 170 175

Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Thr 180 185 190

Asn Gly Ile Leu Phe Cys Gly Arg Phe Ser Ser Pro 195 200

<210> 162

<211> 156

<212> PRT

<213> Homo sapiens

<400> 162

Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu 1 5 10 15

Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met 20 25 30

Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn 35 40 45

Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly 50 60

Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn 65 70 75 80

Lys Thr Gly Thr Gln Tyr Leu Leu Arg Met Ala Asn Arg Leu Phe Gly 85 90 95

Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys

Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu 115 120 125

Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly 130 135 140

Lys Met Tyr Cys Tyr Ser Thr Phe Val Ile Thr Ser 145 150 155

<210> 163

<211> 517

<212> PRT

<213> Homo sapiens

<400> 163

Met Ala Ala Leu Met Thr Pro Gly Thr Gly Ala Pro Pro Ala Pro Gly
1 5 10 15

Asp Phe Ser Gly Glu Gly Ser Gln Gly Leu Pro Asp Pro Ser Pro Glu 20 25 30

Pro Lys Gln Leu Pro Glu Leu Ile Arg Met Lys Arg Asp Gly Gly Arg

Leu Ser Glu Ala Asp Ile Arg Gly Phe Val Ala Ala Val Val Asn Gly 50 60

Ser Ala Gln Gly Ala Gln Ile Gly Ala Met Leu Met Ala Ile Arg Leu 65 70 75 80

Arg Gly Met Asp Leu Glu Glu Thr Ser Val Leu Thr Gln Ala Leu Ala 85 90 95

Gln Ser Gly Gln Gln Leu Glu Trp Pro Glu Ala Trp Arg Gln Gln Leu 100 105 110

Val Asp Lys His Ser Thr Gly Gly Val Gly Asp Lys Val Ser Leu Val 115 120 125

Leu Ala Pro Ala Leu Ala Ala Cys Gly Cys Lys Val Pro Met Ile Ser 130 135 140

Gly 145	Arg	Gly	Leu	Gly	His 150	Thr	Gly	Gly	Thr	Leu 155	Asp	Lys	Leu	Glu	Ser 160
Ile	Pro	Gly	Phe	Asn 165	Val	Ile	Gln	Ser	Pro 170	Glu	Gln	Met	Gln	Val 175	Leu
Leu	Asp	Gln	Ala 180	Gly	Cys	Cys	Ile	Val 185	Gly	Gln	Ser	Glu	Gln 190	Leu	Val
Pro	Ala	Asp 195	Gly	Ile	Leu	Tyr	Ala 200	Ala	Arg	Asp	Val	Thr 205	Ala	Thr	Val
Asp	Ser 210	Leu	Pro	Leu	Ile	Thr 215	Ala	Ser	Ile	Leu	Ser 220	Lys	Lys	Leu	Val
Glu 225	Gly	Leu	Ser	Ala	Leu 230	Val	Val	Asp	Val	Lys 235	Phe	Gly	Gly	Ala	Ala 240
Val	Phe	Pro	Asn	Gln 245	Glu	Gln	Ala	Arg	Glu 250	Leu	Ala	Lys	Thr	Leu 255	Val
Gly	Val	Gly	Ala 260	Ser	Leu	Gly		Arg 265	Val	Ala	Ala	Ala	Leu 270	Thr	Ala
Met	Asp	Lys 275	Pro	Leu	Gly	Arg	Cys 280	Val	Gly	His	Ala	Leu 285	Glu	Val	Glu
Glu	Ala 290	Leu	Leu	Cys	Met	Asp 295	Gly	Ala	Gly	Pro	Pro 300	Asp	Leu	Arg	Asp
Leu 305	Val	Thr	Thr	Leu	Gly 310	Gly	Ala	Leu	Leu	Trp 315	Leu	Ser	Gly	His	Ala 320
Gly	Thr	Gln	Ala	Gln 325	Gly	Ala	Ala	Arg	Val 330	Ala	Ala	Ala	Leu	Asp 335	Asp
Gly	Ser	Ala	Leu 340	Gly	Arg	Phe	Glu	Arg 345	Met	Leu	Ala	Ala	Gln 350	Gly	Val
Asp	Pro	Gly 355	Leu	Ala	Arg	Ala	Leu 360	Суѕ	Ser	Gly	Ser	Pro 365	Ala	Glu	Arg
Arg	Gln 370	Leu	Leu	Pro	Arg	Ala 375	Arg	Glu	Gln	Glu	Glu 380	Leu	Leu	Ala	Pro
Ala 385	Asp	Gly	Glu	Arg	Ser 390	Gly	Glu	Ser	Pro	Ser 395	Phe	Arg	Leu	Arg	His 400
Pro	Leu	Pro	Phe	Pro 405	Arg	Pro	Arg	Pro	Phe 410	Pro	Ser	Pro	Arg	Leu 415	Ser
Ala	Pro	Leu	Pro 420	Ala	Gly	Thr	Val	Glu 425	Leu	Val	Arg	Ala	Leu 430	Pro	Leu
Ala	Leu	Val 435	Leu	His	Glu	Leu	Gly 440	Ala	Gly	Arg	Ser	Arg 445	Ala	Gly	Glu
Pro	Leu 450	Arg	Leu	Gly	Val	Gly 4 55		Glu	Leu	Leu	Val 460	Asp	Val	Gly	Gln
Arg	Leu	Arg	Arg	Gly	Thr	Pro	Trp	Leu	Arg	Val	His	Arg	Asp	Gly	Pro

465 470 475 480

Ala Leu Ser Gly Pro Gln Ser Arg Ala Leu Gln Glu Ala Leu Val Leu 485 490 495

Ser Asp Arg Ala Pro Phe Ala Ala Pro Ser Pro Phe Ala Glu Leu Val500 505 510

Leu Pro Pro Gln Gln 515

<210> 164

<211> 142

<212> PRT

<213> Homo sapiens

<400> 164

Met Ser Asp Ala Ser Leu Arg Ser Thr Ser Thr Met Glu Arg Leu Val 1 5 10

Ala Arg Gly Thr Phe Pro Val Leu Val Arg Thr Ser Ala Cys Arg Ser 20 25 30

Leu Phe Gly Pro Val Asp His Glu Glu Leu Ser Arg Glu Leu Gln Ala 35 40 45

Arg Leu Ala Glu Leu Asn Ala Glu Asp Gln Asn Arg Trp Asp Tyr Asp 50 55 60

Phe Gln Gln Asp Met Pro Leu Arg Gly Pro Gly Arg Leu Gln Trp Thr
65 70 75 80

Glu Val Asp Ser Asp Ser Val Pro Ala Phe Tyr Arg Glu Thr Val Gln
85 90 95

Ile Ser Ser Pro Ser Ala Arg Asp Gln Arg Leu Arg Ser Arg Arg Ala
100 105 110

Met Ser Pro Arg Arg Val Pro Leu Gln Ala Pro Pro Leu Ala Trp Ala 115 120 125

Arg Trp Ser Arg Pro Arg Ala Arg Gly Cys Gly Glu Pro Ile 130 135 140

<210> 165

<211> 561

<212> PRT

<213> Homo sapiens

<400> 165

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile 1 5 10 15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
20 25 30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
35 40 45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val 90 Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala 120 Pro Ser Ser Gly Asp Asp Glu Asp Glu Asp Glu Ala Glu Asp Thr 135 Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp 155 Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys 165 Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly 185 Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His 200 Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly 215 Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr 230 235 Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu 275 Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu 310 315 Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu 325 Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu 360 Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe

370 375 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Xaa Cys Arg Leu Arg Ser 385 390 395 400

Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg 405 410 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser 420 425 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly 435 440 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys 450 455 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu 465 470 475 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys 485 490 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
500 505 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met 515 520 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gln Val 530 535 540

Pro Met Leu Leu Asp Val Thr Ser Leu Tyr Ile Ser Ile Tyr Ile Ile 545 550 555 560

Tyr

<210> 166

<211> 188

<212> PRT

<213> Homo sapiens

<400> 166

Met Asp Pro Ala Arg Pro Leu Gly Leu Ser Ile Leu Leu Leu Phe Leu

1 5 10 15

Thr Glu Ala Ala Leu Gly Asp Ala Ala Gln Glu Pro Thr Gly Asn Asn 20 25 30

Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu

Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe 50 55 60

Leu Tyr Gly Gly Cys Glu Gly Asn Arg Asn Asn Phe Tyr Thr Trp Glu 65 70 75 80

Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys

85 90 95

Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys 100 105 110

Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly 115 120 125

Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr 130 135 140

Cys Met Gly Phe Cys Ala Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser 145 150 155 160

Pro Lys Asp Glu Gly Leu Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe 165 170 175

Asn Ile Asp Val Ser Ile Ser Thr Ala Val Lys Leu 180 . 185

<210> 167

<211> 539

<212> PRT

<213> Homo sapiens

<400> 167

Met Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg
1 5 10 15

Ser Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro 20 25 30

Glu Pro Arg Lys Pro Leu Glu Lys Ala Val Ala Asn Phe Phe Ser Gly 35 40 45

Ser Cys Ala Pro Cys Ala Asp Gly Thr Asp Phe Pro Gln Leu Cys Gln 50 55 60

Leu Cys Pro Gly Cys Gly Cys Ser Thr Leu Asn Gln Tyr Phe Gly Tyr 65 70 75 80

Ser Gly Ala Phe Lys Cys Leu Lys Asp Gly Ala Gly Asp Val Ala Phe 85 90 95

Val Lys His Ser Thr Ile Phe Glu Asn Leu Ala Asn Lys Ala Asp Arg 100 105 110

Asp Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp 115 120 125

Glu Tyr Lys Asp Cys His Leu Ala Gln Val Pro Ser His Thr Val Val 130 135 140

Ala Arg Ser Met Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn 145 150 155 160

Gln Ala Gln Glu His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu 165 170 175

Phe Ser Ser Pro His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His

180 185 190 Gly Phe Leu Lys Val Pro Pro Arg Met Asp Ala Lys Met Tyr Leu Gly 200 Tyr Glu Tyr Val Thr Ala Ile Arg Asn Leu Arg Glu Gly Thr Cys Pro 215 Glu Ala Pro Thr Asp Glu Cys Lys Pro Val Lys Trp Cys Ala Leu Ser 230 His His Glu Arg Leu Lys Cys Asp Glu Trp Ser Val Asn Ser Val Gly 250 Lys Ile Glu Cys Val Ser Ala Glu Thr Thr Glu Asp Cys Ile Ala Lys 265 Ile Met Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Val Tyr Ile Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr 295 Asn Lys Ser Asp Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala 310 315 Val Ala Val Lys Lys Ser Ala Ser Asp Leu Thr Trp Asp Asn Leu 330 Lys Gly Lys Lys Ser Cys His Thr Ala Val Gly Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu Tyr Asn Lys Ile Asn His Cys Glu Pro 355 360 Asn Asn Lys Glu Gly Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu 375 Val Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln 390 Asn Thr Gly Gly Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu 410 Lys Asp Tyr Glu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu 425 Glu Tyr Ala Asn Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val 435 440 Thr Arg Lys Asp Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln 455 Gln His Leu Phe Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys 465 470

Cys Leu Ala Lys Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly
500 505 510

Leu Phe Arg Ser Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val

485

490

Glu Glu Tyr Val Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser 515 520 525

Ser Leu Leu Glu Ala Cys Thr Phe Arg Arg Pro 530 535

<210> 168

<211> 77

<212> PRT

<213> Homo sapiens

<400> 168

Met Arg Thr Leu Leu Pro Pro Ala Leu Leu Thr Cys Trp Leu Leu Ala 1 5 15

Pro Val Asn Ser Ile His Pro Glu Cys Arg Phe His Leu Glu Ile Gln
20 25 30

Glu Glu Glu Thr Lys Cys Ala Glu Leu Leu Arg Ser Gln Thr Glu Lys
35 40 45

His Lys Gly His Thr Lys Gly Phe Ile Leu Ile His Ala Gly Gly Leu
50 55 60

Lys Arg Ile Leu Asp Pro His Thr Tyr Pro Leu Ala Pro 65 70 75

<210> 169

<211> 161

<212> PRT

<213> Homo sapiens

<400> 169

Met Lys Leu Pro Glu Val Cys Phe Phe Asn Cys Cys Thr Leu His Glu
1 5 10 15

Ser Lys Tyr Glu Ile Val Thr Met Phe Ile Tyr Phe Asn Trp Leu Tyr
20 25 30

Phe Phe Pro Ala Asn Gly Phe Gln Val Asp Asn Tyr Gly Thr Gln Leu 35 40 45

Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser 50 . 55 60

Leu Phe Glu Phe His Gly Pro Ser Trp Cys Leu Thr Pro Ala Asp Arg 65 70 75 80

Gly Leu Cys Arg Ala Asn Glu Asn Arg Phe Tyr Tyr Asn Ser Val Ile 85 90 95

Gly Lys Cys Arg Pro Phe Lys Tyr Ser Gly Cys Gly Gly Asn Glu Asn 100 105 110

Asn Phe Thr Ser Lys Gln Glu Cys Leu Arg Ala Cys Lys Gly Phe 115 120 125

Ile Gln Arg Ile Ser Lys Gly Gly Leu Ile Lys Thr Lys Arg Lys Arg

130 135 140

Lys Lys Gln Arg Val Lys Ile Ala Tyr Glu Glu Ile Phe Val Lys Asn 145 150 155 160

Met

<210> 170

<211> 157

<212> PRT

<213> Mouse

<400> 170

Met Tyr Asn Thr Ser Xaa Met Xaa Pro Xaa Asn Pro Arg Pro Ile Leu 1 5 10 15

Thr Ile Ile Thr Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asp
20 25 30

Ser Phe Glu Val Arg Val Cys Ala Ser Pro Gly Arg Asp Pro Arg Thr 35 40 45

Glu Glu Glu Asn Phe Arg Lys Lys Glu Val Leu Cys Pro Glu Leu Pro
50 55 60

Pro Gly Ser Ala Lys Arg Ala Leu Pro Thr Cys Thr Ser Ala Ser Pro 65 70 75 80

Pro Gln Lys Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Lys Ile
85 90 95

Arg Gly Arg Lys Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu 100 105 110

Glu Leu Lys Asp Ala His Ala Thr Glu Glu Ser Gly Asp Ser Arg Ala 115 120 125

His Ser Ser Tyr Leu Lys Thr Lys Lys Gliy Gln Ser Thr Ser Arg His 130 135 140

Lys Lys Thr Met Val Lys Lys Val Gly Pro Asp Ser Asp 145 150 155

<210> 171

<211> 157

<212> PRT

<213> Mouse

<400> 171

Met Phe Asn Arg Ser Cys Leu Arg Gly Met Asn Pro Arg Pro Ile Leu 1 5 10 15

Thr Ile Ile Thr Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asp
20 25 30

Ser Phe Glu Val Arg Val Cys Ala Ser Pro Gly Arg Asp Pro Arg Thr 35 40 45

Glu Glu Glu Asn Phe Arg Lys Clu Val Leu Cys Pro Glu Leu Pro 55 Pro Gly Ser Ala Lys Arg Ala Leu Pro Thr Cys Thr Ser Ala Ser Pro Pro Gln Lys Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Lys Ile Arg Gly Arg Lys Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu 105 Glu Leu Lys Asp Ala His Ala Thr Glu Glu Ser Gly Asp Ser Arg Ala 120 His Ser Ser Tyr Leu Lys Thr Lys Lys Gly Gln Ser Thr Ser Arg His Lys Lys Thr Met Val Lys Lys Val Gly Pro Asp Ser Asp 150 <210> 172 <211> 1252 <212> PRT <213> Mouse <400> 172 Met Gly Ala Ala Ser Gly Gln Arg Gly Arg Trp Pro Leu Ser Pro Pro Leu Leu Met Leu Ser Leu Leu Val Leu Leu Gln Pro Ser Pro Ala Pro Ala Leu Asp Pro Gly Leu Gln Pro Gly Asn Phe Ser Pro Asp Glu Ala Gly Ala Gln Leu Phe Ala Glu Ser Tyr Asn Ser Ser Ala Glu Val Val Met Phe Gln Ser Thr Val Ala Ser Trp Ala His Asp Thr Asn Ile Thr Glu Glu Asn Ala Arg Arg Gln Glu Glu Ala Ala Leu Val Ser Gln 85 Glu Phe Ala Glu Val Trp Gly Lys Lys Ala Lys Glu Leu Tyr Glu Ser 105 Ile Trp Gln Asn Phe Thr Asp Ser Lys Leu Arg Arg Ile Ile Gly Ser 115 120 125 Ile Arg Thr Leu Gly Pro Ala Asn Leu Pro Leu Ala Gln Arg Gln Gln 135 Tyr Asn Ser Leu Leu Ser Asn Met Ser Arg Ile Tyr Ser Thr Gly Lys 155 Val Cys Phe Pro Asn Lys Thr Ala Thr Cys Trp Ser Leu Asp Pro Glu 165 170

Leu Thr Asn Ile Leu Ala Ser Ser Arg Ser Tyr Ala Lys Leu Leu Phe 180 185 Ala Trp Glu Gly Trp His Asp Ala Val Gly Ile Pro Leu Lys Pro Leu 200 Tyr Gln Asp Phe Thr Ala Ile Ser Asn Glu Ala Tyr Arg Gln Asp Asp 215 Phe Ser Asp Thr Gly Ala Phe Trp Arg Ser Trp Tyr Glu Ser Pro Ser 230 Phe Glu Glu Ser Leu Glu His Ile Tyr His Gln Leu Glu Pro Leu Tyr 250 Leu Asn Leu His Ala Tyr Val Arg Arg Ala Leu His Arg Arg Tyr Gly Asp Lys Tyr Val Asn Leu Arg Gly Pro Ile Pro Ala His Leu Leu Gly 280 Asp Met Trp Ala Gln Ser Trp Glu Asn Ile Tyr Asp Met Val Val Pro 295 Phe Pro Asp Lys Pro Asn Leu Asp Val Thr Ser Thr Met Val Gln Lys 305 310 Gly Trp Asn Ala Thr His Met Phe Arg Val Ser Glu Glu Phe Phe Thr 330 325 Ser Leu Gly Leu Ser Pro Met Pro Pro Glu Phe Trp Ala Glu Ser Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val Val Cys His Ala Ser Ala Trp Asp Phe Tyr Asn Arg Lys Asp Phe Arg Ile Lys Gln Cys Thr Arg 375 Val Thr Met Glu Gln Leu Ala Thr Val His His Glu Met Gly His Val 390 385 Gln Tyr Tyr Leu Gln Tyr Lys Asp Leu His Val Ser Leu Arg Arg Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly Asp Val Leu Ala Leu Ser 420 Val Ser Thr Pro Ala His Leu His Lys Ile Gly Leu Leu Asp His Val Thr Asn Asp Ile Glu Ser Asp Ile Asn Tyr Leu Leu Lys Met Ala Leu 455 Glu Lys Ile Ala Phe Leu Pro Phe Gly Tyr Leu Val Asp Gln Trp Arg 470 465 Trp Gly Val Phe Ser Gly Arg Thr Pro Pro Ser Arg Tyr Asn Phe Asp 490 Trp Trp Tyr Leu Arg Thr Lys Tyr Gln Gly Ile Cys Pro Pro Val Ala

500 505 510

Arg Asn Glu Thr His Phe Asp Ala Gly Ala Lys Phe His Ile Pro Asn 515 520 525

Val Thr Pro Tyr Ile Arg Tyr Phe Val Ser Phe Val Leu Gln Phe Gln 530 535 540

Phe His Gln Ala Leu Cys Lys Glu Ala Gly His Gln Gly Pro Leu His 545 550 555 560

Gln Cys Asp Ile Tyr Gln Ser Ala Gln Ala Gly Ala Lys Leu Lys Gln 565 570 575

Val Leu Gln Ala Gly Cys Ser Arg Pro Trp Gln Glu Val Leu Lys Asp 580 585 590

Leu Val Gly Ser Asp Ala Leu Asp Ala Lys Ala Leu Leu Glu Tyr Phe 595 600 605

Gln Pro Val Ser Gln Trp Leu Glu Glu Gln Asn Gln Arg Asn Gly Glu 610 615 620

Val Leu Gly Trp Pro Glu Asn Gln Trp Arg Pro Pro Leu Pro Asp Asn 625 630 635 640

Tyr Pro Glu Gly Ile Asp Leu Glu Thr Asp Glu Ala Lys Ala Asp Arg 645 650 655

Phe Val Glu Glu Tyr Asp Arg Thr Ala Gln Val Leu Leu Asn Glu Tyr 660 665 670

Ala Glu Ala Asn Trp Gln Tyr Asn Thr Asn Ile Thr Ile Glu Gly Ser 675 680 685

Lys Ile Leu Leu Glu Lys Ser Thr Glu Val Ser Asn His Thr Leu Lys 690 695 700

Tyr Gly Thr Arg Ala Lys Thr Phe Asp Val Ser Asn Phe Gln Asn Ser 705 710 1715 720

Ser Ile Lys Arg Ile Ile Lys Lys Leu Gln Asn Leu Asp Arg Ala Val 725 730 735

Leu Pro Pro Lys Glu Leu Glu Glu Tyr Asn Gln Ile Leu Leu Asp Met 740 745 750

Glu Thr Thr Tyr Ser Leu Ser Asn Ile Cys Tyr Thr Asn Gly Thr Cys
755 760 765

Met Pro Leu Glu Pro Asp Leu Thr Asn Met Met Ala Thr Ser Arg Lys 770 780

Tyr Glu Glu Leu Leu Trp Ala Trp Lys Ser Trp Arg Asp Lys Val Gly
785 790 795 800

Arg Ala Ile Leu Pro Phe Phe Pro Lys Tyr Val Glu Phe Ser Asn Lys 805 810 815

Ile Ala Lys Leu Asn Gly Tyr Thr Asp Ala Gly Asp Ser Trp Arg Ser 820 825 830

Leu Tyr Glu Ser Asp Asn Leu Glu Gln Asp Leu Glu Lys Leu Tyr Gln 835 840 845

- Glu Leu Gln Pro Leu Tyr Leu Asn Leu His Ala Tyr Val Arg Arg Ser 850 855 860
- Leu His Arg His Tyr Gly Ser Glu Tyr Ile Asn Leu Asp Gly Pro Ile 865 870 875 880
- Pro Ala His Leu Leu Gly Asn Met Trp Ala Gln Thr Trp Ser Asn Ile 885 890 895
- Tyr Asp Leu Val Ala Pro Phe Pro Ser Ala Pro Asn Ile Asp Ala Thr 900 905 910
- Glu Ala Met Ile Lys Gln Gly Trp Thr Pro Arg Arg Ile Phe Lys Glu 915 920 925
- Ala Asp Asn Phe Phe Thr Ser Leu Gly Leu Leu Pro Val Pro Pro Glu 930 935 940
- Phe Trp Asn Lys Ser Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val 945 950 955 960
- Val Cys His Pro Ser Ala Trp Asp Phe Tyr Asn Gly Lys Asp Phe Arg 965 970 975
- Ile Lys Gln Cys Thr Ser Val Asn Met Glu Asp Leu Val Ile Ala His 980 985 990
- His Glu Met Gly His Ile Gln Tyr Phe Met Gln Tyr Lys Asp Leu Pro 995 1000 1005
- Val Thr Phe Arg Glu Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly 1010 1015 1020
- Asp Ile Met Ala Leu Ser Val Ser Thr Pro Lys His Leu Tyr Ser Leu 1025 1030 1035 1040
- Asn Leu Leu Ser Thr Glu Gly Ser Gly Tyr Glu Tyr Asp Ile Asn Phe 1045 1050 1055
- Leu Met Lys Met Ala Leu Asp Lys Ile Ala Phe Ile Pro Phe Ser Tyr 1060 1065 1070
- Leu Ile Asp Gln Trp Arg Trp Arg Val Phe Asp Gly Ser Ile Thr Lys 1075 1080 1085
- Glu Asn Tyr Asn Gln Glu Trp Trp Ser Leu Arg Leu Lys Tyr Gln Gly
 1090 1095 1100
- Leu Cys Pro Pro Val Pro Arg Ser Gln Gly Asp Phe Asp Pro Gly Ser 1105 1110 1115 1120
- Lys Phe His Val Pro Ala Asn Val Pro Tyr Val Arg Tyr Phe Val Ser 1125 1130 1135
- Phe Ile Ile Gln Phe Gln Phe His Glu Ala Leu Cys Arg Ala Ala Gly
 1140 1145 1150

His Thr Gly Pro Leu His Lys Cys Asp Ile Tyr Gln Ser Lys Glu Ala 1155 1160 1165

Gly Lys Leu Leu Ala Asp Ala Met Lys Leu Gly Tyr Ser Lys Pro Trp 1170 1175 1180

Pro Glu Ala Met Lys Leu Ile Thr Gly Gln Pro Asn Met Ser Ala Ser 1185 1190 1195 1200

Ala Met Met Asn Tyr Phe Lys Pro Leu Thr Glu Trp Leu Val Thr Glu 1205 1210 1215

Asn Arg Arg His Gly Glu Thr Leu Gly Trp Pro Glu Tyr Asn Trp Ala 1220 1225 1230

Pro Asn Thr Gly Thr Thr Pro Thr Leu Pro Pro Ala Pro Ile Leu Trp 1235 1240 1245

Ile Pro Ser Val 1250

<210> 173

<211> 374

<212> PRT

<213> Mouse

<400> 173

Met Thr Met Thr Leu His Thr Lys Ala Ser Gly Met Ala Leu Leu His 1 5 10 15

Gln Ile Gln Gly Asn Glu Leu Glu Pro Leu Asn Arg Pro Gln Leu Lys 20 25 30

Met Pro Met Glu Arg Ala Leu Gly Glu Val Tyr Val Asp Asn Ser Lys 35 40 45

Pro Thr Val Phe Asn Tyr Pro Glu Gly Ala Ala Tyr Glu Phe Asn Ala 50 55 60

Ala Ala Ala Ala Ala Ala Ala Ser Ala Pro Val Tyr Gly Gln Ser 65 70 75 80

Gly Ile Ala Tyr Gly Pro Gly Ser Glu Ala Ala Ala Phe Ser Ala Asn 85 90 95

Ser Leu Gly Ala Phe Pro Gln Leu Asn Ser Val Ser Pro Ser Pro Leu
100 105 110

Met Leu Leu His Pro Pro Pro Gln Leu Ser Pro Phe Leu His Pro His 115 120 125

Gly Gln Gln Val Pro Tyr Tyr Leu Glu Asn Glu Pro Ser Ala Tyr Ala 130 135 140

Val Arg Asp Thr Gly Pro Pro Ala Phe Tyr Arg Ser Asn Ser Asp Asn 145 150 155 160

Arg Arg Gln Asn Gly Arg Glu Arg Leu Ser Ser Ser Asn Glu Lys Gly
165 170 175

Asn Met Ile Met Glu Ser Ala Lys Glu Thr Arg Tyr Cys Ala Val Cys Asn Asp Tyr Ala Ser Gly Tyr His Tyr Gly Val Trp Ser Cys Glu Gly 200 Cys Lys Ala Phe Phe Lys Arg Ser Ile Gln Gly His Asn Asp Tyr Met Cys Pro Ala Thr Asn Gln Cys Thr Ile Asp Lys Asn Arg Arg Lys Ser 225 235 Cys Gln Ala Cys Arg Leu Arg Lys Cys Tyr Glu Val Gly Met Met Lys Gly Gly Ile Arg Lys Asp Arg Gly Gly Arg Met Leu Lys His Lys 265 Arg Gln Arg Asp Asp Leu Glu Gly Arg Asn Glu Met Gly Ala Ser Gly 280 Asp Met Arg Ala Ala Asn Leu Trp Pro Ser Pro Leu Val Ile Lys His 295 Thr Lys Lys Asn Ser Pro Ala Leu Ser Leu Thr Ala Asp Gln Met Val 310 Ser Ala Leu Leu Asp Ala Glu Pro Pro Met Ile Tyr Ser Glu Tyr Asp 330 Pro Ser Arg Pro Phe Ser Glu Ala Ser Met Met Gly Leu Leu Thr Asn 345 Leu Ala Asp Arg Glu Leu Val His Met Ile Asn Trp Ala Lys Arg Val Pro Gly Gly Asn Ser Leu

370

<210> 174

<211> 468

<212> PRT

<213> Mouse

<400> 174

Met Ala Thr Leu Leu Arg Ser Lys Leu Thr Asn Val Ala Thr Ser Val

Ser Asn Lys Ser Gln Ala Lys Val Ser Gly Met Phe Ala Arg Met Gly

Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His Cys Asp

Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile Leu Lys

Ser Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro Val Glu 75

Gly	Asp	Ile	His	Tyr 85	Gln	Arg	Gly	Gly	Ala 90	Pro	Leu	Pro	Pro	Ser 95	Gly
Ser	Lys	Asp	Gln 100	Ala	Val	Gly	Ala	Gly 105	Gly	Glu	Phe	Gly	Gly 110	His	Asp
Lys	Pro	Lys 115	Ile	Thr	Ala	Trp	Glu 120	Ala	Gly	Trp	Asn	Val 125	Thr	Asn	Ala
Ile	Gln 130	Gly	Met	Phe	Val	Leu 135	Gly	Leu	Pro	Tyr	Ala 140	Ile	Leu	His	Gly
145	Tyr				150					155					160
	Thr			165					170					175	
	Glu		180	×				185					190		
	Cys	195					200					205			
	Gln 210					215					220				
225	Gly				230					235					240
	Ser			245	·				250				_	255	
	Lys		260					265					270		
	His	275					280					285			
	Arg 290					295	-		-		300				-
305	Phe				310					315					320
	Phe			325					330					335	
	Cys		340					345			-		350	_	_
	Phe	355					360					365		_	
	Ile 370					375					380				
Phe 385	Leu	Val	Ala	Lys	Ala 390	Leu	Leu	Ser	Tyr	Pro 395	Leu	Pro	Phe	Phe	Ala 400
Ala	Val	Glu	Val	Leu	Glu	Lys	Ser	Leu	Phe	Gln	Glu	Gly	Ser	Arg	Ala

405 410 415

Phe Phe Pro Ala Cys Tyr Gly Gly Asp Gly Arg Leu Lys Ser Trp Gly 420 425 430

Leu Thr Leu Arg Cys Ala Leu Val Val Phe Thr Leu Leu Met Ala Ile 435 440 445

Ser Ser Cys Ala Met Tyr Pro Phe Val Glu Leu Tyr Thr Val Arg Val 450 455 460

Val Cys Ser Trp 465

(19) World Intellectual Property Organization International Bureau



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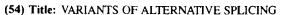
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(57) Abstract: The present invention concerns novel variants, amino acid and nucleic acid sequences obtained by alternative splicing of known sequences, expression vectors and host cells containing the variants' nucleic acid sequence, and antibodies reactive with the variants' products. The invention also concerns pharmaceutical compositions containing any of the above as well as methods of detection. A preferred example is the angiotensin converting enzyme (ACE) variant.

TERMINATIONAL SEARCH KEPUKI

PCT/IL 00/00766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/57 C07K14/47 C07K14/705 C12N9/48
C12Q1/68 G01N33/68 G01N33/50 A61K38/17 A61K38/48

According to International Patent Classification (IPC) or to both national classification and IPC

8. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC - 7 - C07K - C12N - A61K - C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, MEDLINE

,8,9, 0-22 -30 ,8,9,
,8,9,
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-30

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents :	T later document published after the international filling date
"A" document defining the general state of the art which is not considered to be of particular refevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means.	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu
P document published prior to the international filing date but later than the priority date claimed	ments, such combination being obvious to a person skilled in the art. *8" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2001	1 3. 08. 01
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentiaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3018	Andres, S

INTERNATIONAL SEARCH REPORT

lı ational Application No
PCT/IL 00/00766

		PCT/IL 0	0/00/00
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
X	FURLONG T J ET AL: "MOLECULAR CHARACTERIZATION OF A HUMAN BRAIN ADENOSINE A2 RECEPTOR" MOLECULAR BRAIN RESEARCH, vol. 15, no. 1/02, 1 September 1992 (1992-09-01), pages 62-66, XP000615546 ISSN: 0169-328X the whole document		2,8,9
X	DATABASE EM_HUM 'Online! EMBL; Accession number : U40771; ID : HS2AAR02, 15 December 1995 (1995-12-15) "Human A2a adenosine receptor subtype (ADORA2A) gene" XP002165717 abstract		2
A	GELFAND M S ET AL: "ASDB: Database of alternatively spliced genes." NUCLEIC ACIDS RESEARCH, vol. 27, no. 1, 1 January 1999 (1999-01-01), pages 301-302, XP002165716 ISSN: 0305-1048 cited in the application		
Α	CHU Y Y ET AL: "Characterization of the rat A2a adenosine receptor gene." DNA AND CELL BIOLOGY, (1996 APR) 15 (4) 329-37., XP000992998		
X	BERNSTEIN K E ET AL: "THE ISOLATION OF ANGIOTENSIN-CONVERTING ENZYME CDNA" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 263, no. 23, 15 August 1988 (1988-08-15), pages 11021-11024, XP000095152 ISSN: 0021-9258		2,8,9, 32,38,39
Y	the whole document		1-22, 25-53, 56-61
Y	SUGIMURA K ET AL.: "Alternative splicing of the mRNA coding for the human endothelial angiotensin-converting enzyme: a new mechanism for solubilization." BIOCHEM BIOPHYS RES COMMUN 1998 JUN 18;247(2):466-72., XP002173427 the whole document ————————————————————————————————————		1-22, 25-53, 56-61

INTERNATIONAL BEARCH REFORM

Ir ational Application No
PCT/IL 00/00766

		PC1/1L 00/00/00
C.(Continu Category *	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERNSTEIN K E ET AL: "MOUSE ANGIOTENSIN-CONVERTING ENZYME IS A PROTEIN COMPOSED OF TWO HOMOLOGOUS DOMAINS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 264, no. 20, 1989, pages 11945-11951, XP002173428 ISSN: 0021-9258 the whole document	2,8,9, 32,38,39
X	WO 90 03435 A (INST NAT SANTE RECH MED) 5 April 1990 (1990-04-05) the whole document	2,8-13, 32,38-44
X	WO 85 00369 A (CHIRON CORP) 31 January 1985 (1985-01-31) the whole document	2,8,9
X	DATABASE EM_EST 'Online! EMBL; Accession number : AI790464, 4 July 1999 (1999-07-04) MARRA, M. ET AL.: "u101e02.x1 Sugano mouse kidney mkia Mus musculus cDNA clone IMAGE:2064794 3' " XP002173429 abstract	2
Y	WHITE R ET AL: "STRUCTURAL ORGANIZATION AND EXPRESSION OF THE MOUSE ESTROGEN RECEPTOR" MOLECULAR ENDOCRINOLOGY, vol. 1, no. 10, 1987, pages 735-744, XP001002989 ISSN: 0888-8809 the whole document	1-22, 25-30
Y	LU B ET AL: "Estrogen receptor-beta mRNA variants in human and murine tissues." MOLECULAR AND CELLULAR ENDOCRINOLOGY, vol. 138, no. 1-2, 16 March 1998 (1998-03-16), pages 199-203, XP001002992 ISSN: 0303-7207 the whole document	1-22, 25-30
X	KOIKE S ET AL: "MOLECULAR CLONING AND CHARACTERIZATION OF RAT ESTROGEN RECEPTOR CDNA" NUCLEIC ACIDS RESEARCH, vol. 15, no. 6, 25 March 1987 (1987-03-25), pages 2499-2513, XP002026307 ISSN: 0305-1048 the whole document	2,8,9
	-/	

INTERNATIONAL SEARCH REPORT

Im ational Application No PCT/IL 00/00766

		PCT/IL 00/00766
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PFEFFER ULRICH ET AL: "Alternative splicing of the estrogen receptor primary transcript normally occurs in estrogen receptor positive tissues and cell lines." JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 56, no. 1-6, 1996, pages 99-105, XP001002991 ISSN: 0960-0760 the whole document	1-22, 25-30
Т	WO 01 00823 A (EUROP MOLECULAR BIOLOGY LAB; DENGER STEFANIE (IT); FLOURIOT GILLES) 4 January 2001 (2001-01-04)	

INTERNATIONAL SEARCH REPORT

International application No. PCT/IL 00/00766

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Int	ternational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Claims Nos.: 23 24 54 55 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
з. 🗶	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
	1-61 (inventions 1, 30 and 31)
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:
Remark :	on Protest The additional search fees were accompanied by the applicant's protest. X No protest accompanied the payment of additional search fees.

search has been carried out for these claims.

Continuation of Box I.2

Claims Nos.: 23 24 54 55

Present claims 23, 24, 54 and 55 relate to compounds defined by reference to a desirable characteristic or property, namely their capacity to be an activator or deactivator of a particular protein. The claims cover all compounds having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

such as to render a meaningful search impossible. Consequently, no

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: Claims 1-30 (all partially)

A nucleic acid sequence defined by SEQ ID 1 and its corresponding aminoacid sequence SEQ ID 88. An antibody binding specifically to the protein, vectors and hosts expressing the nucleic acid, pharmaceutical compositions containing them and their uses in therapeuty or diagnostic.

- Claims: Invention 2: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 2 and 89.
- Claims: Invention 3: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 3 and 90.
- Claims: Invention 4: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 4,5,91 and 92.
- Claims: Invention 5: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 6 and 93.
- Claims: Invention 6: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 7 and 94.
- Claims: Invention 7: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 8 and 95.
- Claims: Invention 8: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 9,10,96 and 97.
- Claims: Invention 9: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 11 and 98.
- Claims: Invention 10: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 12 and 99.

- 11. Claims: Invention 11: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 13-16 and 100-103.
- 12. Claims: Invention 12: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 17-19,104-106 and 163.
- 13. Claims: Invention 13: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 20,107 and 159.
- 14. Claims: Invention 14: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 21-24,61,62, 108-111,149,150 and 160-162.
- 15. Claims: Invention 15: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 25 and 112.
- 16. Claims: Invention 16: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 26,27,113 and 114.
- 17. Claims: Invention 17: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 28,64,115,152 and 164.
- 18. Claims: Invention 18: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 29,116 and 139.
- 19. Claims: Invention 19: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 30-34,52-55,117-121 and 140-143.
- 20. Claims: Invention 20: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 35,122,170 and 171.

- 21. Claims: Invention 21: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 36 and 123.
- 22. Claims: Invention 22: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 37,38,124,125 and 167.
- 23. Claims: Invention 23: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 39 and 126.
- 24. Claims: Invention 24: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 40,45,46,127, 132,133 and 168.
- 25. Claims: Invention 25: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 41 and 128.
- 26. Claims: Invention 26: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 42,43,48-50, 129,130 and 135-137.
- 27. Claims: Invention 27: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 44 and 131.
- 28. Claims: Invention 28: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 47 and 134.
- 29. Claims: Invention 29: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 51,138 and 165.
- 30. Claims: Invention 30: Claims 1-30 (all partially) and claims 31-61

As for subject 1, but concerning SEQ IDs 56,85,144 and 172.

- 31. Claims: Invention 31: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 57,145 and 173.
- 32. Claims: Invention 32: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 58 and 146.
- 33. Claims: Invention 33: Claims 1-30 (all partially)
 As for subject 1, but concerning SEQ IDs 59 and 147.
- 34. Claims: Invention 34: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 60,148 and 174.
- 35. Claims: Invention 35: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 63 and 151.
- 36. Claims: Invention 36: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 65 and 153.
- 37. Claims: Invention 37: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 66 and 154.
- 38. Claims: Invention 38: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 67 and 155.
- 39. Claims: Invention 39: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 68,69,156,157 and 166.
- 40. Claims: Invention 40: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 70,158 and 169.
- 41. Claims: Inventions 41 to 56: Claims 1-30 (all partially)

 As for subject 1, but concerning SEQ IDs 71-84, 86 and 87

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FURTHER INFORMATION CONTINUED FROM	PCT/ISA/ 210
respectively.	
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Information on patent family members

In ational Application No PCT/IL 00/00766

	nt document search report	t	Publication date		Patent family member(s)	Publication date
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